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THE NATURAL HISTORY OF CHRONIC HEPATITIS (CIRRHOSIS OF THE LIVER).

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Our interest in the evolution of chronic hepatitis (cirrhosis of the liver) was aroused some years ago by the case of a middle aged man in whom at operation following a large gastric hemorrhage there was found not the expected gastric ulcer but a small shrunken cirrhotic liver. The patient had been a vigorous man apparently in perfect health until a few months before his death. He did not use alcohol. The cause of the cirrhosis was obscure until it was brought out that 11 years previously he had had an attack of so-called catarrhal jaundice. The thought seemed not unreasonable that slowly progressive changes in the liver followed this bout of acute hepatitis, in spite of apparent complete recovery, and that when these changes had finally become extreme terminal evidences of cirrhosis rapidly appeared. Stimulated by this observation we realized that little attention had been paid in the literature to the precursors of the later stages of chronic hepatitis (cirrhosis). Addis' studies of Bright's disease have clearly shown[1] the frequency of long latent periods, following the initial insult to the kidneys when for years the subject may appear entirely well, even though proper studies of urinary sediment and of renal function demonstrate a relentlessly progressive lesion which finally results in renal insufficiency and clinical uremia. It is known that such latent periods may be punctuated by clinical exacerbations, and also that the initial stage can be acute and clinically violent (acute nephritis) or entirely below the threshold of clinical observation. We developed a similar concept of hepatitis[3] on a more or less hypothetical basis and the present

purpose is to reinforce the views previously outlined by an analysis of cases which we have actually observed. Most of our conclusions have been reached in the past by others,[2,5,11] but piecemeal, and scattered through the literature; it would seem useful to bring all this material together in "a round unvarnished tale."

Material. During the past 5 years the diagnosis of chronic hepatitis or cirrhosis was made in approximately 100 cases in our clinic. After discarding those in which the diagnosis seemed in doubt and those which were insufficiently observed there remained some 50 well documented records. In each instance some or all of the classical findings were present: hepatic facies, spider angiomata, fetor hepaticus, jaundice, ascites, and induration of liver and spleen. Measurements of blood bilirubin, morphological studies of the blood, and so on were adequate. In many cases the patients were followed over periods of years and finally came to autopsy. We found it impossible clinically to subdivide the cases into various types or diseases; they all conformed in the end to the familiar picture variously spoken of as atrophic, portal, alcoholic or Laennec's cirrhosis. Among 42 patients with advanced cirrhosis 36 gave the usual history of marked alcoholism; otherwise the etiology was entirely obscure.

The Relation of Advanced Hepatitis (Cirrhosis) to an Antecedent Acute Hepatitis. Forty-one patients who were observed in an obviously advanced stage of cirrhosis were thoroughly cross examined as to a possible attack of acute hepatitis in past years. Special emphasis was placed on history of jaundice. The results of this inquiry were strikingly barren. In only 4 cases was there a definite story of an ancient jaundice; in 3 others there was a doubtful history and in 2 others a statement too vague to be trustworthy. Inasmuch as a real attack of icterus is usually remembered and patients err on the side of giving false histories of jaundice (when they have merely been sallow or pale), it seems safe to conclude that acute hepatitis is rarely the precursor of or the initial stage of what later develops into advanced cirrhosis. The conclusion seems of particular interest since it has been pointed out[2,5,11,12] that many people who have had an attack of simple jaundice (acute catarrhal, acute infections) continue for some time—perhaps for years—to show evidence of impaired hepatic function in the form of an elevated blood bilirubin content. It may be that acute simple jaundice really comprises a group of different diseases; at any rate it is impossible at present to differentiate those patients in whom recovery takes place from the few who will progress to extreme lesions. The situation is further complicated by the fact that alcoholism, so important in cirrhosis, bears no special relation to simple acute jaundice.

The following are brief abstracts of the 4 cases in which there was definite history of old jaundice:

Case 1. T. M. (No. A–53249), a 47-year-old markedly alcoholic Spaniard, entered the hospital in 1935 complaining of nosebleed and "yellow eyes." He stated that in 1908 he had been "very yellow all over" and was

sick enough to be in bed for a month. Examination now showed slight icterus with a hard smooth liver down to the umbilicus. No definite ascites. Icterus index 24. Indirect Van den Bergh 4.75 U. Wassermann test negative. Spinal fluid negative. Red blood cells 4.9 M., hemoglobin 99% Sahli, white blood cells 4350.

Impression: Chronic hepatitis. Possible relation of old jaundice to present condition.

CASE 2.—A. McCl. (No. 98890), a 51-year-old markedly alcoholic American, was seen in March, 1937. He gave an unequivocal history of an attack of jaundice 12 years ago but was then well until 1 year ago, when jaundice recurred with general failure and swelling of the abdomen. He had been tapped several times. Examination: A very thin man with big belly full of fluid, hepatic facies, spider angiomata, and icterus. Red blood cells 4.2 M., Hemoglobin 70% Sahli, white blood cells 6300. Icteric index 16, Van den Bergh 4.0 U., Takata-Ara +, Rose Bengal 50% of normal function. Plasma protein 6.25 gm. %. Slight fever.

Impression: It seems highly probable that this disease began with acute hepatitis 12 years ago, with slowly progressive latent changes until clinical symptoms of advanced cirrhosis finally appeared.

CASE 3.—J. G. (No. A–42909), a 39-year-old markedly alcoholic American, entered the hospital in March, 1934, with complaint of gas pains. There was a definite story of jaundice 8 years previously. He says his skin and eyes were intensely yellow for at least a week. After recovery he felt perfectly well and in December, 1932, applied for life insurance; he was told by the examiner that he had cirrhosis, probably on the basis of a palpable liver. A few months later jaundice appeared and his abdomen became full. Examination: Icterus, hepatic facies, hard liver 2 fb. below costal margin, moderate ascites. Red blood cells 3.2 M., hemoglobin 62% Sahli, white blood cells 9800. Icteric index 42, Van den Bergh 10 U., Wassermann test negative. He was observed over a period of a year during which his condition remained essentially unchanged.

Impression.: Acute hepatitis 8 years ago followed by slowly progressive latent changes in liver; diagnosis of cirrhosis made in latent stage during life insurance examination; finally obvious clinical cirrhosis.

CASE 4.—H. P. (No. 129019), a markedly alcoholic Mexican woman, aged 41, entered the hospital in 1935 for "bruise spots" on her body. She gave a definite story of being very yellow all over in 1918 when the doctor said her liver was enlarged and advised operation. In 1924 she was in the Stanford skin clinic for a sebaceous cyst. No general examination was made but there were no complaints to suggest cirrhosis then. On entry in April, 1935, she was slightly icteric and there were large spider angiomata. A hard edge was felt 3 cm. below C. M. and the spleen was palpable. No ascites. Red blood cells 3.9 M., hemoglobin 13.6 gm. %, C. I. 1.0+, M. C. V 101 cu. μ. Van den Bergh 3 U. November, 1935, she became drowsy and ran low fever. Vomited large quantities of blood. Ascites developed. Icteric index 40 U. Died November 14, 1935. *Autopsy:* Extreme cirrhotic process. Dense fibrous strands separating small groups of liver cells. It was the impression that this was the end stage of a very sluggish old process. In this case it seems certain that a lesion existed for a much longer time than the 8 months during which she had symptoms. It seems probable that the attack of hepatitis in 1918 was the initial event followed by a long latent progressive stage.

The course of Cases 1 to 4 is shown graphically in Fig. 1.

Another case illustrates the fact that advanced cirrhosis may follow an old acute hepatitis which never produced any clinical symptoms.

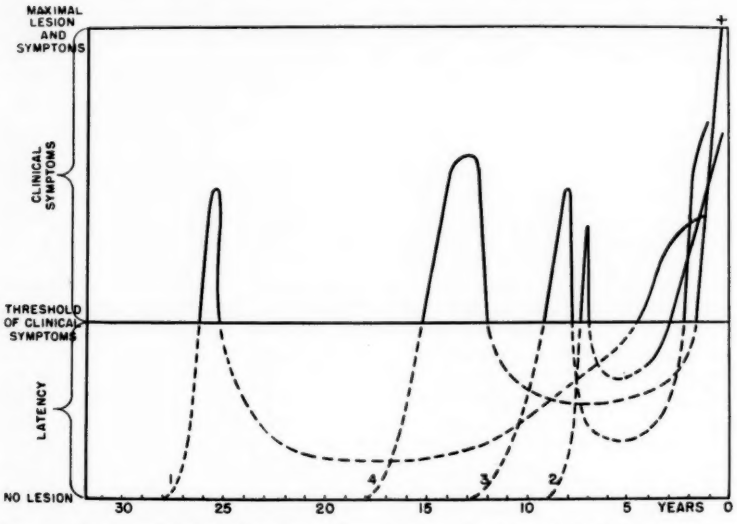

FIG. 1.—Diagram of clinical course of Cases 1 to 4. In this and the following charts that part of the course shown in broken lines is probable but not actually observed.

CASE 5.—N. D. (No. A–19088), a 48-year-old American laborer, had used alcohol to excess. He entered the hospital in January, 1932, with the story that he had always been perfectly well. He had never been jaundiced, nor confined to bed with any acute illness. For several months prior to entry he had failed generally and had lost 20 pounds. One week ago he noticed swelling of the belly. On examination he presented a full-blown picture of advanced cirrhosis with slight icterus, hepatic facies, spider angiomata, palpable hard liver and ascites. Icteric index 20, Van den Bergh 3 U., Wassermann test negative. After a few days he became stuporous and died in coma. At autopsy, there was found indisputable evidence of an ancient acute hepatitis in the form of a so-called healed acute yellow atrophy. The liver weighed 880 gm., was brownish and shrunken with irregular yellow nodules. The brown areas showed scar tissue and bile ducts with no parenchymal cells, and functioning liver tissue was represented only by the scattered yellow nodules. How long ago the attack of acute hepatitis occurred is obscure, but it undoubtedly led in the end to the picture of advanced cirrhosis with liver insufficiency.

This case corresponds quite accurately with those described by Pratt and Stengel,[9] by Goodpasture[13] and others as healed acute yellow atrophy leading to toxic cirrhosis (Mallory). The clinical picture at the end was however in no way distinguishable from the ordinary terminal stage of Laennec's cirrhosis.

The etiology of all the above cases is uncertain; whether alcohol alone is responsible seems problematical.

Evidence that Latent Hepatitis May Exist for Long Periods. The statistics presented in the previous section show that it is a rare event for the changes which eventuate in progressive cirrhosis to be initiated by a clinical attack of acute hepatitis. In fully 80 to 90%

of the present series the first clinical symptoms were those associated with a process already far advanced. It seems probable, then, that in cirrhosis of the Laennec's type there is usually no violent destruction of the liver but a lesion which from the start may be sluggishly progressive over a long period of time. That this is in fact the case we were able to demonstrate in 2 cases in which definite evidences of latent hepatitis were detected 8 and 11 years respectively before clinical symptoms appeared. In this connection we define the latent stage as that in which, if there are any abnormal findings, elevation of blood bilirubin and induration of liver or spleen exist without any departure from health. The presence of toxic symptoms, visible jaundice, ascites, or hematemesis remove the case from the latent to the clinically active group.

CASE 6.—A. J. (No. 182627), a 40-year-old markedly alcoholic Italian, was first seen in 1928 with the complaint of kernels in the neck. A lymph node showed chronic adenitis which seems of no further significance in the case. During the general physical examination a firm liver edge was felt 2 cm. below the costal margin, and the edge of the spleen was palpable. No visible jaundice. Blood count normal. For the next 8 years he was clinically well and active, and it was only by deliberate search that the evidences of a gradually progressive but latent cirrhosis were detected:

June, 1930, liver 3 to 4 cm. below C. M., smooth and firm; R. B. C. 4.5 M., Hb. 82%, Icteric index 20 U., Van den Bergh 2.5 U. April, 1931, liver unchanged. May, 1933, liver unchanged; spleen felt 4 cm. below C. M.; R. B. C. 4.7 M., Hb. 90%, M. C. V. of red cells 98 cu. μ; average R. B. C. diam. 7.8 μ; icteric index 13 U. Van den Bergh 1.25 units. September, 1933, icteric index 24 U.; Van den Bergh 4.5 U. December, 1933, icteric index 24 U.; R. B. C. 4.6 M., Hb. 93%, M. V. C. 105 cu. μ. March, 1934, icteric index 13 U. June, 1934, icteric index 16 U. September, 1934, liver and spleen as before; icteric index 15; feels perfectly well. June, 1935, condition unchanged; R. B. C. 4.8 M., Hb. 95%, M. C. V. 95 cu. μ, Van den Bergh 0.75 U. November, 1936. Entered hospital with complaint of swelling of abdomen and legs for 4 months. During this time had become weak and short of breath. There had been some blood in the stools. On examination, he was slightly undernourished and there was fetor hepaticus. The belly was distended with fluid. Liver 2 cm. and spleen 15 cm. below costal margin. R. B. C. 3.9 M., Hb. 75%, W. B. C. 5000. Icteric index 24 U. Van den Bergh 7.5 U. Rose Bengal 26% of normal function. Slight elevation of temperature. He was tapped several times but rapidly became toxic and died on February 3, 1937. *Autopsy* showed very advanced cirrhosis of the portal type.

This case is reported somewhat at length, but it is of unusual interest. Over 8 years we observed, after accidental discovery, induration of liver and spleen with slight hyperbilirubinemia in a man clinically well. A pathological increase in red blood cell size was definite 3 years before symptoms developed. Finally, there was rapid onset of clinical signs of advanced cirrhosis and death in coma within 8 months.

CASE 7.—E. C. (No. 67081), a 70-year-old Italian who denied the use of alcohol, was first seen in the clinic in 1918 for a mild nephritis and hypertension. At that time a firm liver was felt 3 cm. below C. M. and the spleen

was readily palpable. The red blood count was normal but there was a constant leukopenia of 2000 to 3000. There were no clinical symptoms of hepatitis but in 1926, 8 years later, he was in the hospital for a slight cerebral accident. The liver and spleen were as before and now there was a slight hyperchromic anemia with R. B. C. 3.6 M., Hb. 73%, C. I. 1+, W. B. C. 2100. It was not until February, 1929, 11 years after he was first seen, that clinical symptoms of liver disease appeared and he entered because of swollen abdomen and weakness of several months' duration. After tapping, a very hard liver was felt in the epigastrium. R. B. C. 4.8 M., Hb. 82%, W. B. C. 6000, icteric index only 8 U., and Van den Bergh 0.25 U. There were repeated taps but he died of general failure in April, 1929.

It seems clear that a gradually progressive hepatitis had existed for a great many years.

In both Cases 6 and 7 the recognition of latent hepatitis was made possible by the fortuitous chance of the patients' coming under observation for complaints unrelated to the liver disease. It seems probable that signs of insidious hepatic lesions could be detected in many people who eventually appear with advanced cirrhosis were there an opportunity of making physical examinations during antecedent years. The course of Cases 6 and 7 is shown in Fig. 2.

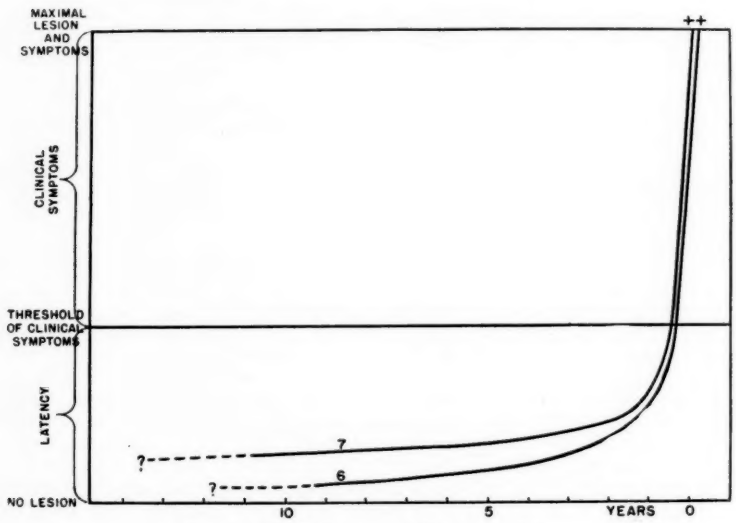

FIG. 2.—Clinical course of Cases 6 and 7.

Acute Exacerbations During the Course of Chronic Hepatitis and the Difficulty of Differentiation from Initial Acute Attacks. The etiology of acute hepatitis is obscure except in those cases which follow certain drugs or poisons, and in those occurring in epidemic form, probably the result of infectious agents (epidemic jaundice, Weil's disease, yellow fever). The cause of the common variety of sporadic hepatitis seen in civil practice is still a mystery. Patho-

logical material is scanty but there is good reason to believe that one may be dealing with a group and not with a single disease. Certainly there are a variety of clinical types. The classical "catarrhal jaundice" is usually a mild disease showing little more than the presence of icterus and perhaps a palpable liver. Recovery is the rule and even though a slight hyperbilirubinemia may persist for a considerable period this type of disease rarely, as we pointed out above, goes on to progressive chronic hepatitis. At the other end of the scale are those instances of obscure necrosis of liver cells—acute yellow atrophy—usually fatal in a few weeks. But cases of every degree of severity between these two extremes seem to occur and recent papers have dealt with acute hepatitis associated with ascites and evidences of great "toxemia" which may heal or at least be followed by clinical recovery.[4,8] It is this type of disorder which we wish now to discuss in its relations to hepatitis as a whole—both acute and chronic. Of particular interest is the distinction between fresh initial attacks and acute exacerbations of chronic hepatitis. The cases described below show that it is often impossible to make a clinical differentiation.

I. Cases Probably or Certainly Representing Initial Attacks of Hepatitis.

Clinical picture indistinguishable from advanced chronic hepatitis, but in fact an initial attack of acute hepatitis running its entire course to death in coma in 4 months.

CASE 8.—C. P. (No. A–44622), a moderately alcoholic Italian woman aged 36, had always been well. In April, 1934, she was thoroughly examined in connection with the diagnosis of a mild skin lesion. There was nothing then to suggest liver disease. Hb. 75%, R. B. C. 4.1 M., W. B. C. 6900. She returned to the clinic 8 months later (December 12, 1934), with a story of increasing swelling of abdomen and jaundice for 3 months. She was now obviously icteric and the liver was enlarged to the level of the umbilicus, smooth and slightly tender. The spleen was not felt. There was high irregular fever. R. B. C. 2.3 M., Hb. 8.2 gm. %, C. I. 1.0+, M. C. V. 115 cu. μ, icteric index 50 U., Van den Bergh 5 U., W. B. C. 33,000, P. M. N. 87%. December 26, 1934, exploratory laparotomy. There was a large quantity of ascitic fluid, the gall bladder was normal, the spleen was firm and twice normal size. The liver was large and had a stippled appearance. Biopsy showed subacute cirrhosis—not the picture of acute yellow atrophy. Cultures from bile and abdominal fluid were sterile. She continued to run high fever after operation, jaundice persisted, ascites reaccumulated, there was progressive macrocytic anemia. She gradually went into coma and died January 12, 4 months after initial symptoms.

Discussion. The story of alcoholism and the clinical features were typical of an advanced chronic cirrhosis. The negative examination 4 to 5 months before onset of symptoms and the histology of the liver make it clear however that one was really dealing with a rapidly progressive initial attack of hepatitis. The etiology of this type of liver disease, clinically quite different from the usual variety of

"catarrhal jaundice" and anatomically not acute yellow atrophy, is obscure. The case corresponds to those described by Jones and Minot,[7] and others.

Acute hepatitis with jaundice and ascites undistinguishable at first from advanced cirrhosis. Biopsy—subacute yellow atrophy. Clinical recovery. Question of residual damage.

CASE 9.—I. W. (No. A–66297), an American woman, aged 58, who denied use of alcohol, was well until September 20, 1936, when she was taken with abdominal soreness and weakness and later nausea and jaundice. On entrance into hospital, October 12, she appeared ill, there was definite icterus, and a deeply placed mass in R. U. Q., probably liver. October 21 exploratory laparotomy showed the liver to be small, grayish, scarred and irregular. Biopsy showed an acute hepatitis with diffuse necrosis of liver cells. After operation there was increase of nausea, intense jaundice with icteric index 200 U., Van den Bergh 60 U., and ascites. She was tapped twice. R. B. C. 3.9 M., Hb. 80% Sahli, C. I. 1.0+, W. B. C. 7000, M. C. V. 93 cu. Average diam. of R. B. C. 8.8 μ, Wassermann test negative. She seemed desperately ill but made an unexpected recovery and left the hospital on November 24, only 6 weeks after entry. At that time she was still slightly jaundiced but there was no reaccumulation of fluid. In May, 1937, she returned for study. She was apparently perfectly well. Physical examination was negative except that tip of spleen was palpable. R. B. C. 4.2 M., Hb. 84% Sahli, icteric index 7 U., Van den Bergh 0.5 U., M. C. V. 88 cu. μ., Rose Bengal showed very slight delay in abstraction of dye from blood; estimated function 70% of normal.

Discussion. This case is of interest as the third instance in our series of hepatitis with jaundice and ascites with recovery. It seems practically certain that this was an initial attack of hepatitis, now in a healed or latent stage. Further observation is necessary to see whether there will be progression to chronic hepatitis.

Acute hepatitis probably initial, but possibly exacerbation of an old process.

CASE 10.—R. S. (54895), a 55-year-old German who denied use of alcohol, entered hospital on June 24, 1935, with the complaint of jaundice and nausea for 5 weeks. He was thin, markedly icteric, the liver was enlarged and there was ascites. R. B. C. 3.5 M., Hb. 70% Sahli, M. V. C. 134 cu. μ, icteric index 125 U., Van den Bergh 25 U. Exploratory laparotomy 3.L fluid, gall bladder normal. Biopsy of liver showed atrophy of periportal cells with increase in connective tissue and proliferation and dilation of bile capillaries. He gradually improved and by July 31 seemed definitely on the road to recovery. Icteric index down to 25 U., M. C. V. of R. B. C. still 112 cu. μ. On August 1 a seminal vesiculotomy was done for some old trouble and he died 2 days later of postoperative complications. *Autopsy:* Spleen weighed 350 gm. Liver cut with increased resistance. There was central necrosis with increase in peripheral connective tissue which was infiltrated with round cells. Anatomical diagnosis: subacute hepatitis.

Discussion. It is extremely difficult to decide whether the hepatitis is recent or old but the histology of the liver suggests a fairly recent process. It seems probable therefore that one is dealing with an initial attack which was, clinically at least, subsiding when an ill advised operation upset his balance.

II. Instances of Probable or Certain Acute Clinical Exacerbations of a Chronic Hepatitis.

Old "alcoholic" hepatitis with acute exacerbation of symptoms practically indistinguishable from an initial attack.

CASE 11.—G. P. (No. A–58592), a 57-year-old German-American liquor salesman, had drunk heavily for 30 years, but his general health had been very good. Three weeks before entrance on November 14, 1935, he noticed rapid swelling of the abdomen and jaundice. On examination he was obese, there was light icterus and an immense collection of abdominal fluid. After tapping, a hard liver edge was felt 2 cm. below costal margin. R. B. C. 3.9 M., Hb. 70%, M. V. C. 101 cu. μ, average diameter 8.1 μ. Wassermann test negative. Icteric index 34 U., Van den Bergh 3.75 U., Rose Bengal 20% of normal function. Takata-Ara +, blood urea 63 mg.%. He was extremely ill and stuporous from entry to January, 1936, and was tapped frequently. Gradual improvement then set in. He was tapped repeatedly for the next few months but in March, 1937, no tap had been necessary for 19 weeks and only 3 L. were obtained. No reaccumulation 3 weeks later (June, 1937). Icteric index 8 U., Van den Bergh 1 U. Feels perfectly well—firm liver edge just palpable.

Discussion. It seems probable that one is dealing here with an acute exacerbation of an old hepatitis, but the differentiation from an initial attack is practically impossible.

Terminal exacerbation of old chronic hepatitis clinically indistinguishable from an initial attack.

CASE 12.—A. H. (No. A–71212), a 59-year-old American woman, had used alcohol heavily for years. Recently she had eaten very little and had practically lived on gin and tea. There was nothing in the past history otherwise to suggest liver disease. Present illness began 3 weeks before entry on May 13, 1937, with weakness, nausea, and vomiting. Jaundice for 1 week. Examination showed an obese sick woman, markedly jaundiced, the skin covered with "bruise spots." Ascites was present and a very hard irregular liver was felt. R. B. C. 2.9 M., Hb. 72% Sahli, C. I. 1.2, W. B. C. 8800, M. C. V. 112 cu. μ., platelets 107,000. Bleeding time indefinitely prolonged. Coagulation time 9 minutes. Icteric index 81 U., Van den Bergh 25 U. No autodigestion of blood clot. Rose Bengal 20% of normal function. Wassermann test negative. She failed rapidly and died in coma May 26, about a month after onset of symptoms. Autopsy showed an extreme cirrhosis of a very chronic type. The changes were undoubtedly of great duration. There were no evidences of acute liver degeneration.

Discussion. Clinically the case is indistinguishable from those instances of initial hepatitis reported above, but here one is undoubtedly dealing with a terminal clinical exacerbation of an old chronic process.

III. Cases in Which it Was Impossible to Decide Between Initial Acute Hepatitis or Acute Exacerbation of an Old Hepatitis.

Acute hepatic coma with jaundice and ascites in a chronic alcoholic. Remarkable recovery. Question whether it is a case of initial acute hepatitis or an acute exacerbation during the course of chronic hepatitis.

CASE 13.—S. F. (No. A–43139), a markedly alcoholic American woman, aged 44, was first seen in the clinic in March, 1934, for tonsillectomy. Examination at that time showed no evidence of liver disease although there was no specific note on the abdomen. She was perfectly well until October, 1934, when she was brought to the hospital in coma. Relatives gave the

story that she had been on numerous alcoholic debauches but was not ill until 2 weeks before entry when she was taken in the night with epigastric distress, nausea and vomiting. On examination, she presented the typical picture of hepatic coma: jaundice, fetor hepaticus, large spider angiomata and ascites. She was tapped twice for 650 cc. and 950 cc. There was moderate fever. R. B. C. 2.8 M., Hb. 11.3 gm. %, C. I. 1.2, M. C. V. 109 cu. μ, average R. B. C. diameter 7.9 μ, Wassermann test negative, icteric index 30, Van den Bergh 3 U., blood urea 217 mg. %. She appeared moribund but under parenteral glucose and saline rapidly improved and left the hospital 18 days after entry practically well. The blood urea had fallen to 25 mg. % and icteric index to 10 U., and the blood count was R. B. C. 4.4 M., Hb. 14.9 gm., M. C. V. 96 cu. μ. There was no reaccumulation of ascitic fluid and the liver edge was felt just below C. M.

She returned 2 years later in October, 1936, for study. She had been perfectly well and looked the picture of health. The spider angiomata had disappeared. No ascites. Liver and spleen not felt. R. B. C. 4.7 M., Hb. 78% Sahli, M. C. V. 92 cu. μ., icteric index 4 U., Van den Bergh 0.5 U., Rose Bengal test showed delayed removal of dye from blood giving an estimated hepatic function of 42%.

Discussion. With the history of alcoholism and the clinical findings it seemed quite certain when she was first seen that one was dealing with advanced cirrhosis and terminal hepatitic coma. The extraordinary recovery with continued good health raises the question of whether she did not have an initial acute hepatitis. The Rose Bengal test suggests a residual liver damage, but there is no other evidence of hepatitis now. Of interest are the very high blood urea without signs of nephritis, the disappearance of large spider angiomata as she recovered (a phenomenon which we have never seen before) and the development of transient macrocytic anemia. This last feature has been noted by Rosenberg[10] and others in similar cases.

Jaundice and ascites in an alcoholic. Question of acute exacerbation in the course of chronic hepatitis or initial attack.

Case 14.—M. S. (No. 167400), an American laborer, aged 28, had used alcohol freely. He had always been well until 3 weeks ago when he had abdominal discomfort and noticed distention of abdomen and jaundice. On entry, September 1, 1927, there were dilated venules over face, spider angiomata, jaundice, ascites and a firm liver extending a hand's breadth below C. M. There was slight elevation of temperature. R. B. C. 4.7 M., Hb. 83% Sahli, Wassermann test negative. Icteric index 96 U., Van den Bergh 12.5 U. He was tapped and improved rapidly. On discharge, September 22, there was no reaccumulation of fluid, jaundice had disappeared (Van den Bergh 0.5 U.), the temperature was normal and the liver was definitely smaller.

Discussion. Unfortunately it was not possible to follow this patient. In view of the alcoholic history the question comes up whether this was an exacerbation of a latent hepatitis or an initial acute attack with recovery. Recovery from hepatitis with ascites is said to be excessively rare and McCabe and Hart[8] were able to collect only 10 instances from the literature. This patient, however, is only one of a number of such cases in the present series.

Question of initial attack of hepatitis or acute exacerbation of chronic cirrhosis. Clinical recovery with residual signs of latent hepatitis.

CASE 15.—A. A. (No. A–61907), a 42-year-old American fireman, gave a history of extreme alcoholism. He had frequently been suspended from the fire department for drunkenness. He entered the hospital April 10, 1936, for an injury to his ankle 1 week before, unaware of jaundice. On examination, there was typical alcoholic facies, spider angiomata on chest, a smooth liver 4 cm. below C. M. and marked icterus. There was moderate fever and the jaundice became more intense. On April 15 the icteric index was 270 U. and the Van den Bergh 70 U. He rapidly developed a severe macrocytic anemia with R. B. C. 1.8 M. and Hb. 44% Sahli. Average diameter of R. B. C. 8.7 μ and M. C. V. 125 cu. μ, W. B. C. 17,000. Wassermann test negative. Bleeding time 9 minutes. Under rest, parenteral fluids and glucose and liver extract there was remarkable improvement and he left the hospital on May 26 feeling perfectly well. At that time icteric index was only 6 U., R. B. C. 3.4 M., Hb. 68%, W. B. C. normal. No fever, The liver was still palpable. On June 23 he went back to work. April, 1937, in hospital for study. Appears perfectly well. Spider angiomata still present. Liver and spleen not felt. R. B. C. 4.4 M., Hb. 92%, C. I. 1.0+, W. B. C. 6400, icteric index 8 U. Van den Bergh 1 U., M. C. V. 91 cu. μ. Rose Bengal test shows definite delay in removal of dye—liver function estimated as 65% of normal.

Discussion. It is impossible to say whether this was an initial attack of hepatitis or an acute exacerbation of a chronic cirrhosis. At any rate, in spite of clinical recovery there remains definite evidence of latent chronic hepatitis.

This group of cases seems of particular importance in an analysis of the life history of hepatitis. One should emphasize the short length of time necessary for the full blown clinical picture of cirrhosis to develop following an initial attack of hepatitis, the fact that the first clinical evidences of a long standing hepatitis may be those of a terminal "toxemia" which leads to death in a few weeks; and finally how all but impossible it often is to distinguish between initial attacks of hepatitis and clinical exacerbations of an old latent cirrhosis. This leads to a discussion of repeated acute exacerbations and remissions during the course of chronic hepatitis. Cases similar to ours have been well described by Fiessinger, Albot and Thiebaut.[6]

CASE 16.—B. B. (No. 181668), a 53-year-old markedly alcoholic Italian, always well previously, stated that 4 years ago he was in another hospital for swollen abdomen and legs. He was tapped several times, but after some months the swelling disappeared and he was perfectly well and working for $3\frac{1}{2}$ years. For the past few weeks there had been loss of weight, indigestion, and recently jaundice and swelling of the abdomen. Examination (November 7, 1928) showed a picture of advanced cirrhosis—icterus, spider angiomata and ascites. R. B. C. 3.0 M., Hb. 61%, C. I. 1.0+, Wassermann test negative. Icteric index 30 U., Van den Bergh 4.5 U. By November 26, 1929, he was much improved, abdominal fluid did not reaccumulate and he felt well but still had slight icterus and anemia. He did very well until January 25, 1930—an interval of a year—when he was brought in after rapid onset of semicoma. He was quite jaundiced but there was no ascites. Liver not felt but spleen palpable. Under treatment he improved slightly but died in April, 1930, in typical hepatic coma. *Autopsy* showed typical changes of advanced cirrhosis.

Discussion. Here there were clearly several clinical exacerbations and remissions. The course is best visualized by the diagram (Fig. 3).

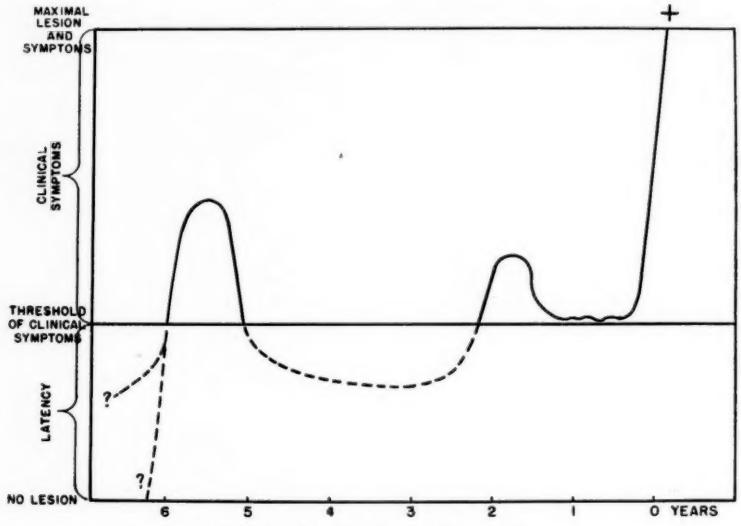

FIG. 3.—Clinical course of Case 16.

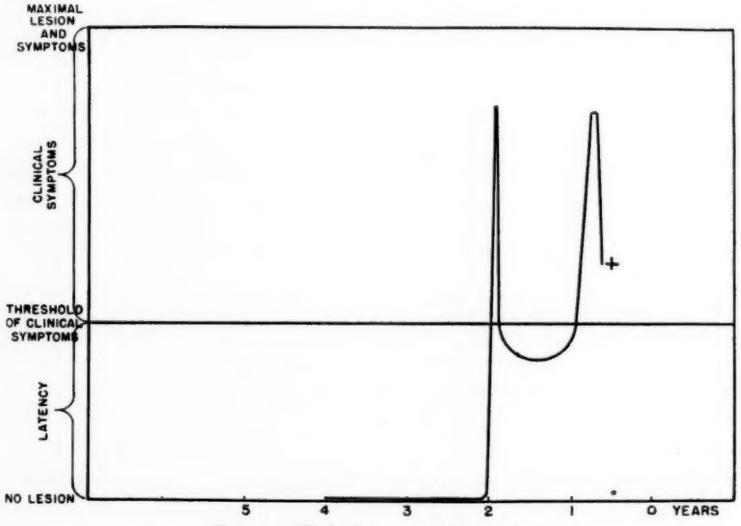

FIG. 4.—Clinical course of Case 17.

CASE 17.—C. D. (No. A–23476), a 59-year-old markedly alcoholic American, was first seen in May, 1932, for injury to his hand. At that time there was no suggestion of liver disease and neither liver nor spleen was felt. Wassermann test negative. Blood count normal. He was well

until February, 1934, when he entered the hospital for epigastric pain of a few days' duration. He looked ill, there was high fever, light icterus and a tender liver a few cm. below C. M. W. B. C. 25,000, icteric index 31 U. He improved quickly and within 3 weeks was discharged with normal temperature and leukocyte count, and icteric index of 6 U. Gastro-intestinal Roentgen rays were negative and liver was no longer palpable. He was entirely well for a year until January, 1935, when he returned with complaint of epigastric pain and fever for 3 days. Exploratory laparotomy, January 22, showed the liver to be scarred, nodular and brick red. Biopsy was done. Gall bladder normal. He improved rapidly and by January 31 seemed on the road to recovery when there was sudden exitus from pulmonary embolus. *Autopsy*—subacute diffuse portal cirrhosis.

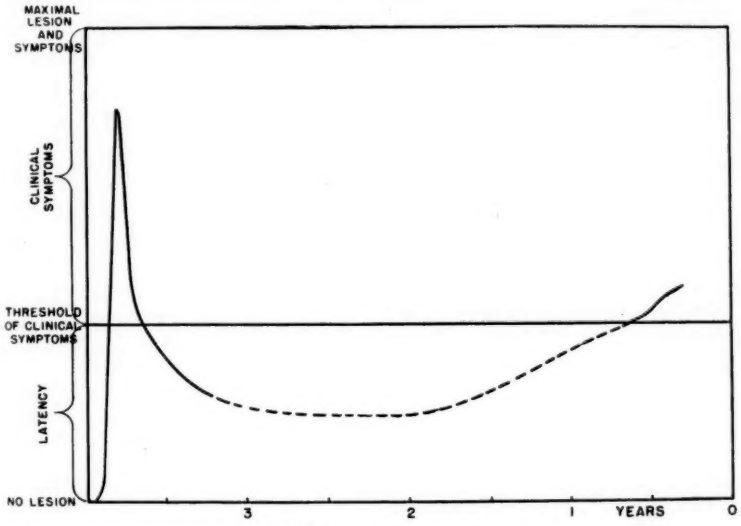

FIG. 5.—Clinical course of Case 18.

Discussion. The course of events is shown graphically in the diagram (Fig. 4). It seems clear that the episode in 1934 was an initial acute attack of hepatitis followed by apparent recovery (but probably actually a latent state with residual damage) until the second acute exacerbation a year later, from which again he seemed to be recovering. The histologic findings make it clear that the disease was of longer duration than the last acute attack, in which he died in less than a month from onset of symptoms.

CASE 18.—H. P. (No. A–39763), a moderately alcoholic American, aged 51, stated that he had been jaundiced for 1 week in 1927 but otherwise had been well. In November, 1933, he entered the hospital with the story of an acute illness of 5 weeks' duration featured by chills, abdominal pain, nausea, vomiting, and recently jaundice. On examination, there was marked icterus and a firm smooth liver was felt 3 cm. below C. M. R. B. C. 3.9 M., Hb. 13.4 gm. %, C. I. 1.0, W. B. C. 5700, M. C. V. 101 cu. μ., Wassermann test negative. Icteric index 111 U., Van den Bergh 25 U. Slight fever, not above 38° C. He improved gradually and by February, 1934, he felt well. Icteric index was 7.5 U. Liver edge still palpable. He

remained subjectively perfectly well for 3 years until May, 1937, when he returned with the story of swelling of legs and enlargement of abdomen for 2 months. On examination, he was a little under weight and there were small spider angiomata. Liver no longer palpable, soft edema of legs. Plasma protein 6.2 gm. %. Icteric index 19 U., Van den Bergh 5 U., R. B. C. 3.9 M., M. C. V. 89 cu. μ.

Discussion. The story of jaundice in 1927, while not definite suggests an attack of hepatitis then. After a remission of 6 years he had, in 1933, an exacerbation under our observation with clinical recovery for 3 years and finally a third recurrence of obvious clinical disease. The situation is summarized in the diagram (Fig. 5).

In addition to such clear cut instances of exacerbation and remission many illustrations could be given of patients whose course varies from better to worse without any extreme fluctuation, and for no assignable reason.

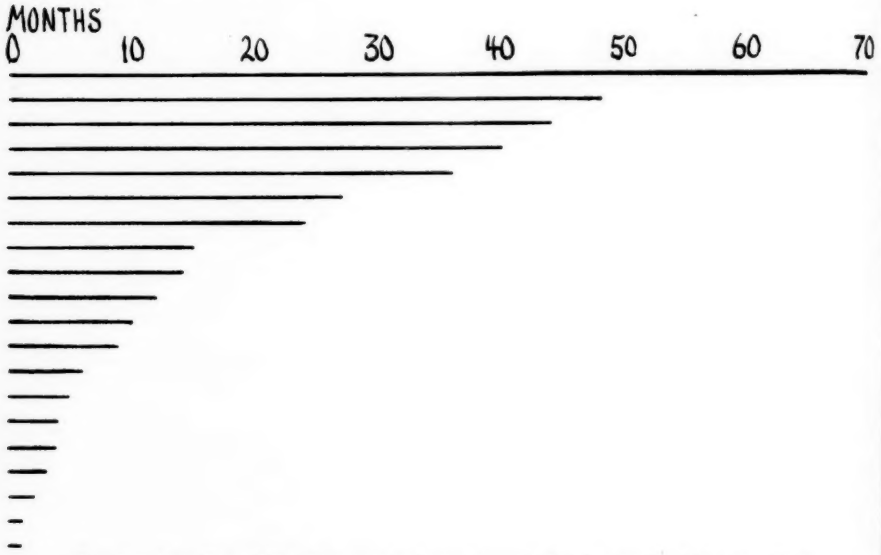

FIG. 6.—Duration of life after onset of symptoms in fatal cases of cirrhosis. Each line is a different patient.

Terminal Stage. There remain for discussion certain clinical aspects of the terminal stage. To simplify the analysis we have segregated all of our cases in which after a latent period of unknown duration death occurred in the first accession of clinical symptoms and autopsy showed advanced cirrhosis. The causes of death were the familiar ones—bleeding, intercurrent infection, postoperative accidents and hepatic coma. The duration of life after onset of clinical symptoms is shown graphically in Fig. 6. The striking finding is that in this series of 20 cases, 45% of the patients died within a year and 40% within 6 months. This shows to what an

extent latent chronic hepatitis may progress before clinical trouble becomes evident.

Discussion. In the preceding pages we have attempted to build up a composite picture of the life history of those obscure instances of hepatitis which are still of unknown etiology. Cases due to assignable cause (aside from the possible influence of alcohol), such as poisons, drugs and known infections, are not included in this discussion which must necessarily then be largely clinical and empirical. The relation of the type of anatomic lesion to the course of the disease will be analyzed in another paper. None of our observations is entirely novel but it seems worth while to synthesize information about hepatitis, which for the most part is scattered in the literature or has not been sufficiently emphasized.

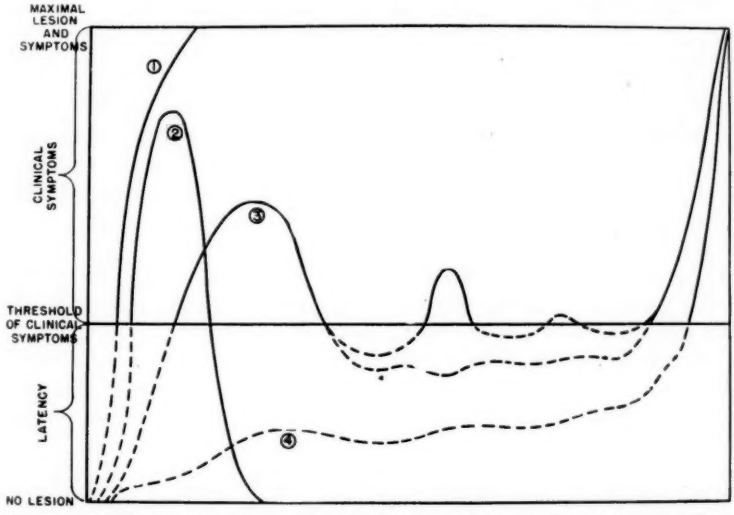

FIG. 7.—Variations in the course of hepatitis. (1) Acute hepatitis progressing rapidly to death. (2) Acute hepatitis with recovery. (3) Acute hepatitis with apparent recovery but actually transition to latent stage which with or without remissions eventuates in advanced cirrhosis. (4) Hepatitis latent from the start until advanced liver insufficiency supervenes.

The initial stage of hepatitis may be clinically acute and promptly fatal. This group includes not only cases of so-called acute yellow atrophy but also instances of a less violently destructive process. An equally acute onset may be followed by complete clinical recovery and probably by healing of the lesion, although it is hard to prove that latent anatomical changes are not present. The possibility of such latent changes, which may gradually progress over many years until clinical hepatic insufficiency supervenes, is shown by those instances of late cirrhosis in which a story of acute hepatitis years ago can be elicited. As illustrated by some of the cases reported above, recognizable but clinically latent disease can be

detected and actually observed over long periods. In our series, it was striking that the initial stage of the common variety of advanced hepatitis (Laennec's cirrhosis) was usually latent; in some 90% of the cases there never was any early clinical episode but both lesion and symptoms were latent until the final crash of hepatic insufficiency. The latent periods may be punctured by clinical exacerbations which again subside into latency, and thus such a cycle may be repeated a number of times before the patient dies. The main possibilities are shown graphically in Fig. 7, and the analogy to the course of glomerular nephritis as analyzed by Addis is brought out.

Conclusions. 1. Cirrhosis of the liver is usually the terminal stage of a long disease which runs most of its early course without clinical symptoms.

2. In the present series, the disease was initiated by an acute clinical attack of hepatitis in only 4 of 41 cases (10+%). In most of the patients the onset was entirely obscure.

3. Acute clinical exacerbations may occur during the course of a progressive latent hepatitis to be followed by further periods of latency.

4. Such acute exacerbations are often indistinguishable from initial attacks of acute hepatitis.

5. Acute hepatitis may run a rapid course with the development in a few weeks or months of the clinical picture usually associated with advanced cirrhosis. Clinical recovery may take place in these cases.

6. In the case of patients with prolonged chronic hepatitis (cirrhosis) who die in their first clinical exacerbation the course is usually brief; in about one-half the cases not over 1 year from onset of symptoms to death.

7. A composite picture of the life history of acute and chronic hepatitis of obscure origin is presented by means of diagrams and illustrative cases.

NOTE.—Throughout this paper the term acute hepatitis is used in a non-committa sense insofar as the exact lesions and their etiology are not entirely clear. Acute hepatitis, however, seems a better term than catarrhal jaundice, simple jaundice or infectious jaundice and preserves the analogy with obscure disease of other organs such as nephritis, arthritis, etc.

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THE EFFECT OF BENZEDRINE SULPHATE ON THE BOWEL AND UTERUS.

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Benzedrine (benzyl methyl carbinamine), a volatile vasoconstrictor allied chemically to ephedrine, was introduced primarily for topical application to the nose and throat in the treatment of congested mucosal surfaces.[2] Benzedrine sulphate, a salt of the base, is soluble in water and has been found active when given by mouth in doses ranging between 5 and 20 mg., although larger doses have been used under controlled circumstances. The conception that benzedrine sulphate might prove advantageous in gastro-intestinal spasm and colic has apparently arisen by analogy with the effect of epinephrine. Sympathetic relaxation of the bowel by epinephrine is a well-known pharmacologic reaction and benzedrine is a sympathomimetic substance. Myerson and Ritvo[5] and Myerson, Loman and Dameshek[6] have proposed that benzedrine sulphate is of value in relieving gastro-intestinal spasm, basing their conclusion on clinical observations aided in some instances by Roentgen ray visualization in man. On the other hand, Peoples and Guttmann[7] could find no symptomatic evidence of any effect of benzedrine sulphate on the gastro-intestinal tract of man. Detrick, Millikan, Modern and Thienes[3] found that benzedrine sulphate actually contracted isolated segments of small intestine of rabbits and guinea-pigs. Also in rats, receiving large doses of benzedrine sulphate, Ehrich and Krumbhaar[4] frequently found postmortem markedly contracted segments of small intestine. In the face of this conflicting evidence, it was considered advisable to repeat the experiments of Detrick *et al.*[3] and in addition to study the effect of benzedrine sulphate on another organ containing smooth muscle, the uterus. The results obtained amply confirm the results of Detrick, Millikan, Modern and Thienes.[3] While this does not necessarily mean that benzedrine sulphate will also contract the human intestine, it is obvious that further work should be done on man.

Method. Short segments of small intestine were taken from freshly killed rabbits and the uterine horns from freshly killed virgin guinea-pigs. Rhythmic contractions of bowel were found much better if the small intestine was moderately filled with warm Locke's solution before removing the segments. The bowel segments and uterine horns were set up in Locke's solution in a side arm test tube connected with a U-thistle tube and surrounded by a water bath maintained at 35° to 37° C. according to the Magnus technique and rhythmic contractions were recorded kymographically. After satisfactory records of normal contractions had been obtained, benzedrine sulphate, ephedrine hydrochloride and epinephrine hydrochloride were added to the warm Locke's solution about the bowel or uterus to a concentration of 0.01 to 0.001%. The record obtained was analyzed to determine the effect of these sympathomimetic substances on the tonus (base line) and rate and strength of rhythmic contractions of the smooth muscle.

TABLE 1.—THE EFFECT OF BENZEDRINE SULPHATE, EPHEDRINE HYDROCHLORIDE AND EPINEPHRINE HYDROCHLORIDE ON ISOLATED SEGMENTS OF SMALL INTESTINE OF RABBITS AND THE VIRGIN GUINEA-PIG UTERUS.

Value.	Benzedrine.			Ephedrine.			Epinephrine.		
		Contractions.			Contractions.			Contractions.	
	Tonus.	Rate.	Strength.	Tonus.	Rate.	Strength.	Tonus.	Rate.	Strength.
Small Intestine.									
Mean (% change) . . .	+49	−5	+14	+22	+2	+94	−65	−13	−25
Standard deviation . .	32	13	30	40	16	78	19	30	29
% cases like change in mean	100	71	59	65	59	77	100	71	71
Uterus.									
Mean (% change) . . .	+52	+21	+66	+64	+24	+60	−94	−100	−100
Standard deviation . .	22	36	101	22	26	61	9	0	0
% cases like change in mean	94	55	55	100	80	80	100	100	100

Results. (Table 1.) All changes in the record were calculated in per cent of the original before application of the salts studied. The averages of these changes are given in Table 1. To illustrate the variation in the changes, the standard deviation of the means have been included and to indicate the consistency of the reaction, the percentage of experiments in which the changes observed were in the same direction as that of the mean has also been determined. It is usually recognized statistically that a mean change in order to be significant should be at least twice its standard deviation. In a number of instances shown in Table 1, the standard deviation was greater than one-half of the mean and yet nearly 100% of the experiments showed a change in the same direction. For example, the tonus of 100% of bowel segments was increased by benzedrine, the average increase was 49% and the standard deviation of the average increase was 32%. In this instance the increase in tonus was obviously significant, but the calculated mean was not typical of the group; in other words, there was considerable variation in the *extent* of the increase in tonus. In all instances the mean values were those of 15 to 20 experiments.

Benzedrine invariably produced a prolonged contraction of the longitudinal muscle of the small intestine and of the smooth muscle of the uterus. Since this change raised the base line from which rhythmic contractions started, it was recorded as an increase in tonus. The rate and strength of rhythmic contractions from this elevated base line were not significantly different after application of the benzedrine sulphate. The predominant feature of the action

of benzedrine was thus a prolonged, spastic type of contraction of the smooth muscle of these organs.

The action of ephedrine was essentially similar to that of benzedrine though not quite as consistent. Epinephrine, on the other hand, relaxed the smooth muscle and inhibited practically all rhythmic contractions. The difference was a striking one and demonstrated clearly that benzedrine and ephedrine have not the same effect as epinephrine on the smooth muscle of the gut and uterus in these 2 species. In this respect, benzedrine and ephedrine differ from meta-synephrine, another related sympathomimetic substance, which relaxes the uterus and bowel like epinephrine.[1]

Previous cocainization of the surviving bowel segments if anything increased the inhibition by epinephrine; but the stimulation produced by benzedrine and ephedrine was less after cocaine hydrochloride. In this set of 17 experiments, the average rise in tonus produced by benzedrine previous to cocaine was 51% and after cocaine it was 37%; corresponding values for ephedrine were +40% and +15% and for epinephrine −80% and −100% respectively. The contractions produced by benzedrine and ephedrine were thus not increased by cocainization, suggesting that their action was not entirely, if at all, on the nerve endings of the motor sympathetic system.

This conclusion was confirmed by further experiments on the reaction following ergotamine tartrate on isolated bowel segments. There was no consistent change in the effect of benzedrine on rabbit small intestine after ergotamine, the average effect being a slightly decreased stimulation both by benzedrine and ephedrine. Epinephrine was slightly more depressant after ergotamine. It is obvious therefore that benzedrine does not act upon the motor sympathetic nerve endings in the rabbit small intestine.

Nor was the effect related to the parasympathetic system. Previous abolition of parasympathetic influence by atropine had no consistent effect on the action of either benzedrine or ephedrine on the surviving bowel segments of rabbits. From these experiments and in the light of present conceptions of sympathetic and parasympathetic reactions, it may be concluded that benzedrine in the concentrations used in this study contracts the smooth muscle of the intestine of rabbits and of the uterus of guinea-pigs by a direct action upon the muscle fibers.

In one experiment, benzedrine contracted a rabbit uterus with a pregnancy of about 2 weeks' duration. In another experiment, the urinary bladder of a guinea-pig was contracted by all 3 of benzedrine, ephedrine and epinephrine, while a spleen from a guinea-pig failed to respond to any of the 3 substances.

Summary. Benzedrine sulphate (concentrations of 0.01 to 0.001%) was found to produce a prolonged, spastic contraction of strips of the smooth muscle of the uterus of virgin guinea-pigs and isolated segments of small intestine of rabbits. From experiments

following ergotamine, cocaine and atropine, it was concluded that this action was directly upon the smooth muscle fibers.

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SYMPTOMATIC TREATMENT OF CHRONIC ENCEPHALITIS WITH BENZEDRINE SULPHATE.

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This paper deals with the clinical results observed in 20 patients with chronic encephalitis having a Parkinsonian syndrome treated with benzedrine sulphate (benzylmethylcarbinamine), 18 of whom have been receiving the drug by mouth for a period of from 6 to 12 months.

Solomon and Prinzmetal[3] have employed the drug in postencephalitic Parkinsonism and reported the results obtained in 28 cases with classical symptoms. Improvement was noted in 53% when benzedrine sulphate was used alone and in 93% when it was given in conjunction with stramonium or scopolamine. Of this group, 22 were able to do more work; 20 observed a decrease in their muscular rigidity; 19 said they felt stronger; 7 observed a decrease or disappearance of their tremor, 9 noticed no change in tremor and the other 12 did not have tremor. In 8 patients with oculogyric crisis, the attacks were eliminated in 6 and greatly diminished in the other 2 when benzedrine was given in addition to scopolamine and stramonium. The drug was found of no value in arteriosclerotic Parkinsonism.

In considering the rationale for its use in these conditions, it may be pointed out that in Parkinsonism we see definite evidence of autonomic dysfunction based on hypothalmic lesions. The drugs of greatest value in postencephalitic Parkinsonism are stramonium, atropine and hyoscine, all of which are said to exert their activity by a sedative action on the parasympathetic side of the autonomic nervous system, although a central brain stem effect must also be considered. The disturbed sleep mechanism so often observed in this disease can probably be accounted for on the same anatomic basis. It has been shown experimentally by Dikshit[1] that injection of acetylocholine, a parasympathetic stimulant, into the ventricles

TABLE 1.—EFFECT OF BENZEDRINE SULPHATE ON PARKINSONIAN SYNDROME IN 20 CASES.

Case. Sex. Age	Outstanding symptoms.	Duration of symptoms in years.	Previous medication continued.	Benzedrine sulphate daily, amount (mg.).	Blood pressure before and after treatment.	Pulse rate before and after treatment.	Weight before and after treatment.	Results of treatment.
1 M 60	Salivation, tremor rt. hand, myoclonus of eyelids	6	Hyoscine Tr. stramonium	50 10 mos.	B 110/70 A 124/70	B 72 A 64	B 145 A 145	Eye sympt. disappeared, more alert and cheerful.
2 M 33	Oculogyric crises, rigidity, slight tremors	8	Hyoscine Tr. stramonium	40 7 mos.	B 85/60 A 112/68	B 105 A 105	B 123 A 128	No subjective or objective improvement.
3 M 49	Generalized rigidity, tonic elevation left shoulder, "grunting"	9	Tr. stramonium	40 12 mos.	B 110/80 A 110/80	B 112 A 96	B 153 A 157	Less rigidity, "grunting" decreased, more alert and cheerful.
4 F 21	Rigidity rt. leg, oculogyric crises, irritability	6	Tr. stramonium	25 6 mos.	B 90/50 A 120/56	B 90 A 84	B 122 A 126	Oculogyric crises controlled more cheerful, less irritable, less rigidity.
5 M 49	Marked rigidity and tremors, salivation, myoclonus eyelids	7	Tr. stramonium	40 12 mos.	B 120/90 A 120/90	B 120 A 112	B 135 A 143	Myoclonus eyelids less marked, salivation diminished, more cheerful and alert.
6 F 35	Rigidity, oculogyric crises, headache, drowsiness, salivation	5	Hyoscine	40 9 mos.	B 88/60 A 88/60	B 72 A 80	B 209 A 209	Fewer and less severe oculogyric crises.
7 F 36	Rigidity, tremors, depression	4	Tr. stramonium	50 10 mos.	B 90/60 A 110/60	B 80 A 80	B 146 A 145	Improvement in mood: not maintained.
8 M 47	Rigidity, tremors	3	Hyoscine	15 1 wk.	B 100/60	B 88	..	Tremors aggravated, refused to continue medication.
9 M 29	Rigidity, tremors, depression	8	Tr. stramonium	30 7 mos.	B 88/60 A 110/78	B 78 A 94	B 125 A 121	Much more cheerful and alert, more energy, less rigidity.
10 F 30	Salivation, tremors, rigidity	8	Atropine	30 8 mos.	B 98/60 A 92/60	B 100 A 110	B 85 A 88	Much more active, alert and cheerful, less rigidity.
11 M 50	Obesity, somnolence, marked tremors	6	Tr. stramonium	20–40 12 mos.	B 120/85 A 120/85	B 80 A 80	B 283 A 267	Somnolence controlled, more alert and cheerful.
12 M 52	Salivation, rigidity, oculogyric crises	7	Tr. stramonium	40 11 mos.	B 125/90 A 100/78	B 128 A 80	B 114 A 114	Oculogyric crises less frequent and severe, less salivation, more energy.
13 F 29	Rigidity, tremors, fatigue, oculogyric crises	5	Tr. stramonium	25 9 mos.	B 100/76 A 110/90	B 112 A 108	B 137 A 126	Fewer oculogyric crises, less tremor, more energy, more cheerful.
14 M 21	Slight rigidity, irritability, periods of excitement	2	Atropine	15 6 mos.	B 110/80 A 110/80	B 100 A 94	B 113 A 110	Distinct improvement in mood, no periods of excitement in 6 mos.
15 M 37	Rigidity, weakness, mental clouding	4	Atropine	20 9 mos.	B 130/72 A 130/78	B 120 A 118	B 142 A 144	More alert and cheerful, more energy.
16 M 38	Salivation, tremors, rigidity	7	Tr. stramonium	50 5 mos. 25 7 mos.	B 80/? A 90/70	B 110 A 110	B 107 A 113	More alert and cheerful, much more energy.
17 M 47	Weakness, rigidity, salivation, drowsiness	1	Atropine	90 8 mos. 30 7 mos.	B 110/70 A 120/90	B 82 A 82	B 120 A 112	Salivation controlled, distinctly more alert and cheerful.
18 M 44	Tremors, rigidity, somnolence	5	Hyoscine	20 1 wk.	.....	..	..	Tremors aggravated, subjectively much worse, refused to continue medication.
19 F 28	Rigidity, weakness, tremors, depression	5	Atropine	15 7 mos.	B 100/70 A 116/70	B 78 A 104	B 112 A 112	Slightly more cheerful, otherwise no change.
20 F 26	Severe oculogyric crises, headache, rigidity, tremors	4	Tr. stramonium	50 7 mos.	B 100/75 A 98/62	B 115 A 100	B 162 A 162	Oculogyric crises shorter and less severe, tremors slightly aggravated.

or hypothalamic region in rats produces a condition resembling normal sleep. Benzedrine, a sympathetic stimulant, or more accurately an adrenalergic drug, exerts its effect in part by enhancing the activity of the drugs, which are parasympathetic sedatives. The Ziskinds[4] in a recent article call attention to the fact that phenobarbital in ordinary therapeutic doses aggravates certain types of rigidity, probably because of its action on the brain stem. They also raise the question as to whether or not physiologic antidotes for the barbiturates may not have a salutary effect in the treatment of the plastic type of rigidity. Benzedrine can be considered such an antidote. Nathanson,[2] studying the effect of benzedrine on a large group of normal individuals, found that it has a definite stimulating action on the higher centers of the central nervous system in most persons besides producing a peripheral response.

Since May, 1936, benzedrine sulphate has been administered to a group of patients with chronic epidemic encephalitis in the Neurologic Out Patient Department of this hospital. Twenty have been treated and followed for a sufficiently long period to justify a report of the clinical observations. These patients were studied from the standpoint of the effect of the drug on specific symptoms, blood pressure, pulse rate and weight. Pertinent data relative to the cases treated is summarized in the accompanying table.

Comment. The blood pressures and pulse rates indicated in the table represent basic levels before and after treatment and not merely isolated readings. Unusually high or low readings were not taken as representative of the true state of the cardiovascular mechanism but evaluated in each individual case.

It was found that many of these patients tend to have a low blood pressure accompanied by a rapid pulse rate which may be only a manifestation of their general state of debilitation, although autonomic imbalance probably accounts for this in part. Those individuals with an initial low blood pressure which increased in response to therapy, as a rule, showed an accompanying decrease in pulse rate and were the patients who acquired greater energy and strength.

Discussion. Of the 20 patients studied, 15 (75%) have shown definite sustained improvement which must be attributed to benzedrine alone, since no change was made in the medical régime which was previously being carried out. In 1 other case some sustained improvement has been noted, but in view of an alteration in the previous medication this cannot be attributed entirely to the benzedrine therapy. One case was better at first but improvement has not been maintained. One patient has not been helped and 2 claim that their symptoms were definitely aggravated by the drug and refused to continue taking it. The improvement noted has not always been the same in every case. Oculogyric crises were controlled or diminished in frequency and severity in 5 of 6 cases. In 2 patients with myoclonus of the eyelids the symptom was greatly benefited. Thirteen patients have manifested a distinct

improvement in mood, have become more cheerful and state that they have more energy. There has been a lessening of rigidity and tremor in a number of patients but this has not been constant and is difficult to evaluate clinically. In 4 cases salivation has become less troublesome. Systolic blood pressure has been raised 10 points or more in 9 patients, has not varied more than 10 points in 8 and was reduced more than 10 points in 1 instance. The remaining 2 patients did not take the drug long enough to provide reliable data. An initial low blood pressure was found in the majority of these patients, 11 having a systolic pressure below 100. The maximum sustained pressure rise in any case was 30 degrees systolic and 20 degrees diastolic. The patients whose blood pressure has been raised materially are in most instances the ones whose pressure was originally low.

The pulse rate was lowered more than 5 beats per minute in 8 patients, did not vary more than 5 points in 6, and was increased in 4 cases. Reliable data were not available in 2. Since the maximum effect of the drug, as manifested by changes in the blood pressure and pulse rate, is said to occur from 10 minutes to 1½ hours after administration and is continued for several hours, the recorded readings were made near the height of the reaction since they were made between 10.30 and 12 in the morning and the largest daily dose of the drug was directed to be taken at 8 A.M.

There was a gain in weight of 1 pound or more in 7 patients, weight remained unchanged in 5, there was weight loss in 6, and no data in 2. The loss in weight, with 1 exception, was not troublesome and occurred in patients who were originally somewhat overweight. The patient who lost the most weight was the man who took 90 mg. of benzedrine daily for 5 months. The weight loss ceased when the dose was decreased to 30 mg. daily but the symptomatic improvement has been maintained. There is much to suggest that doses in excess of 40 to 50 mg. daily are not required to obtain maximum benefits. In this patient and several others there appeared to be an accumulative action or increasing sensitivity to the drug as indicated by the side effects since it became necessary to lower the dosage to avoid sleeplessness and gastro-intestinal symptoms in the form of vomiting. In no instance were the side effects sufficiently troublesome to necessitate discontinuing the administration of benzedrine. Two patients complained of burning on urination with some difficulty in starting the stream but these symptoms cleared spontaneously in 1 case and disappeared on withdrawal of the drug for 2 days in the other without recurrence. However, a medical colleague reports that after taking 30 mg. of benzedrine during a period of stress and strain with physical exhaustion he experienced an adrenalergic reaction characterized by tachycardia, hypertension (pressure rise 25 mm., systolic), dilated pupils, insomnia, nausea and vomiting, and suppression of urine for an 18-hour period. His condition was such as to require hospitalization.

The results of the studies made so far have been encouraging and suggest further investigations. Although a large percentage of these patients have been benefited, the improvement can hardly be other than symptomatic and it is questionable how long it will be maintained. It is not possible at this time to evaluate how much improvement has been based on psychogenic factors, but an attempt will be made to determine this by the use of a placebo in a group of controls. Patients repeatedly reported an aggravation of symptoms when they were without the drug for a few days. In addition, studies of the effect of the drug in this series of patients may help to throw light on its possible efficacy in other types of illness.

Conclusions. 1. Of 20 patients with chronic encephalitis having a Parkinsonian syndrome who received benzedrine sulphate for a period of from 6 to 12 months, 75% have shown definite symptomatic improvement.

2. The symptoms beneficially affected were not the same in every case, but collectively included lessening of rigidity, tremor, salivation and oculogyric crisis. In addition, there was improvement in mood and an increase of strength and energy.

3. Benzedrine enhances the effect of stramonium, atropine and hyoscine and is best used in conjunction with these drugs in the treatment of postencephalitic Parkinsonism.

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THE EXPERIMENTAL PATHOLOGY OF ERGOTISM.

WITH REFERENCE TO SOME NEWER ERGOT DERIVATIVES.*

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Interest in ergot continues to follow identification of the several alkaloids, 12 thus far, particularly since the isolation of ergonovine†

* This investigation was aided by a grant from John Wyeth and Brother, Inc., Philadelphia.

† Within a few months of one another in 1935 the following ergot alkaloids were described: ergometrine (Dudley and Moir[4]), ergostetrine (Thompson[11]), ergobasine (Rothlin[10]) and ergotocine (Davis *et al.*[3]). These were proven later to be identical and the name "ergonovine" was adopted by the Council of Pharmacy and Chemistry of the American Medical Association.

which is the principle responsible for the prompt and vigorous contraction of uterine musculature. It appears, from the pharmacologic standpoint, that the ergot alkaloids can be divided into two general groups, represented by ergotoxine and ergonovine; the former acts mainly on smooth muscle of blood-vessels and has a delayed and relatively weak but protracted oxytocic effect, the latter invoking a rapid but more evanescent uterine response. The clinical implications of ergot fractionation are based on that fundamental difference, particularly in the treatment of migraine (ergotamine tartrate, a member of the ergotoxine group) and in the *status post partum* (ergonovine). Recently ergonovine has assumed importance in migraine therapy as well.[8]

Soon after the isolation of ergonovine (1935) several commercial preparations appeared which were standardized for their content of the alkaloid. One of these, ergoklonin (Wyeth), containing 1 mg. of ergonovine per cc. and freed of the bulk of the ergotoxine group, was subjected to clinical trial in the obstetrical wards of the Philadelphia General Hospital[12] and has been adopted for routine use, supplanting fluid extract of ergot. The experimental work reported here was begun at that time, primarily to determine the safety of the preparation.

Conflicting reports concerning the production of gangrene in the cock's comb with ergonovine have been published. Brown and Dale[1] noted a quite normal comb after injecting 65 mg. intramuscularly over a period of 5 days, although each injection was followed by deep cyanosis and the usual general symptoms. Davis *et al.*,[2] however, injected 6 cocks with 0.5 mg. of "ergotocin" twice daily for 24 days and stated, "One bird developed gangrene of the comb in 8 days, another in 5 days, and still another had a similar lesion 15 days after the completion of the injections." The melting point of the alkaloid used in the latter experiment was slightly different from that of Brown and Dale, due possibly to impurity, thus accounting perhaps for the varied result. An editorial comment[6] warned of the possibility of gangrene from ergonovine, but I know of no such instance resulting from its clinical administration. Ergotamine tartrate has produced gangrene in patients with sepsis or liver disease;[5,9,13] Lennox,[8] however, has found it safe in a large group of cases being treated for migraine, some over a period of almost 5 years.

Regarding the mechanism of ergot gangrene it was not until 1935 that a thorough investigation was published. Lewis and Gelfand,[7] studying "The Manner in Which Necrosis Arises in the Fowl's Comb Under Ergot Poisoning," using ergotoxine ethanesulphonate, reported: "Gangrene of the hen's comb can be produced regularly by day to day injections of 10 mg. ergotoxine into the breast muscles. A constriction of the arteries, which is unrelieved by relaxing vasoconstrictor tone or by local warming, is thereby maintained and, though a little flow of blood continues, serious nutritional

changes occur by the end of a few days. The endothelium of the vessels suffers, plasma is lost and stasis occurs in the capillaries, vascular clotting follows in central vessels, which are by this time dilated, and necrosis is determined. All these changes can be produced within a few days by mechanically impeding the blood flow to the comb. Vascular spasm in ergot poisoning does not arrest the circulation, and so does not cause gangrene directly. The spasm profoundly slows the blood stream and leads to the secondary changes in the vessels described; these are responsible for the arrest of blood flow, which in turn results in death of the tissues."

Drugs Employed.* In order to evaluate any possibility of ergotism through administration of ergoklonin, 3 concentrations of the drug were used, normal (as prepared for clinical use), twice normal and 4 times normal, the stronger solutions being concentrated *in vacuo*. The pure alkaloid, ergonovine (0.5 mg./cc.), and fluid extract of ergot, U. S. P., were employed for comparison.

Standardization of Animals. Ergotoxine ethanesulphonate in a 1% aqueous solution of tartaric acid was prepared in the strength of 0.5 mg./cc. Of this, 0.15 mg./kg. body weight was given each of the animals (white Leghorn cocks acceptable for U. S. P. ergot assay) intramuscularly. Comb response to this "bluing dose" was recorded as 0, 1, 2, 3, individually for each third, anteriorly to posteriorly, no animal being used which had a reaction less than 011, nor more than 223, as observed 15 minutes after injection. This eliminated birds which were either unusually tolerant or hypersensitive to ergot.

Procedure. Cocks were housed under uniform conditions, mostly caged singly, but a few in pairs, with adequate maintenance feeding. The several groups received intramuscular injections of the following drugs, the dose being twice the volume of the "ergotoxine bluing dose" except in Group 4 which is doubled:

Group.	Drug.	No. of animals.	Dose (cc./kg.)	Ergonovine equivalent. (mg./kg.)
1	Fluid extract of ergot (twice daily)	11	0.6	
2	Ergoklonin (normal concentration) (twice daily)	10	0.6	0.06
3	Ergoklonin (concentrated 2×) (twice daily)	9	0.6	0.12
4	Ergoklonin (concentrated 4×) (twice daily)	5	1.2	0.48
5	Ergonovine (twice daily)	2	0.6	0.30
6	Ergonovine (4 times daily)	3	0.6	0.30

* Supplied by Wyeth; the ergonovine was crystallized and the solution prepared by Dr. M. R. Thompson, Professor of Pharmacology, University of Maryland.

PLATE I.

A, Normal control: White Leghorn cocks acceptable for U. S. P. ergot assay. *B*, Standardization: Reaction 1–2–3, 15 minutes after intramuscular injection of ergotoxine ethanesulphonate (0.15 mg./kg. body weight). *C*, Fluid extract of ergot: Moderate atrophy and gangrene produced by intramuscular injection of 1.02 cc. twice daily for 15 days (No. 115). *D*, Fluid extract of ergot: Marked atrophy and gangrene with loss of digitations 6 and 7 produced by intramuscular injection of 0.72 cc. twice daily for 15 days (No. 134). *E*, Ergonovine: Deep cyanosis 1 hour after injection; cock had received 0.7 mg. intramuscularly 4 times daily during the previous 29 days (No. 170). *F*, Ergonovine: Same animal 4 hours after the reaction shown in *C*; there is very slight residual cyanosis (No. 170).

PLATE I

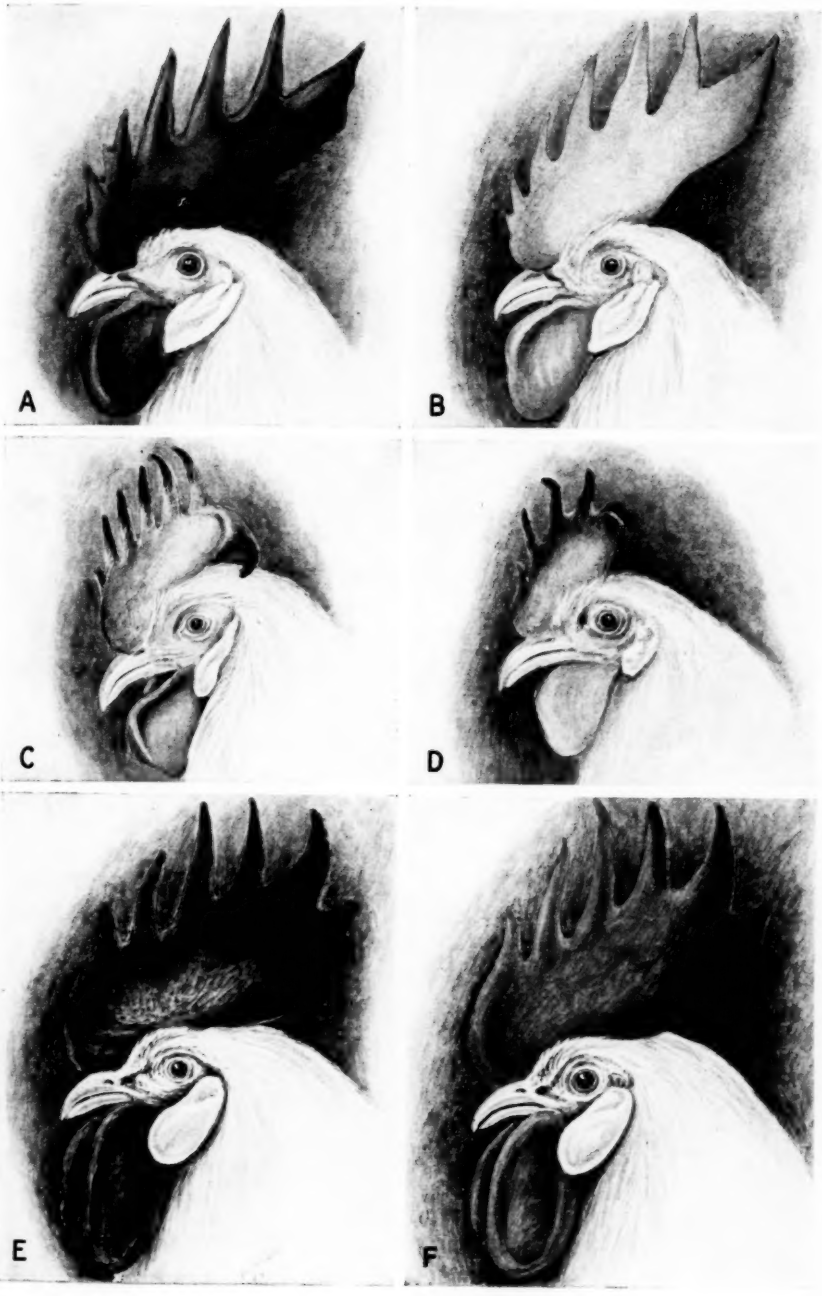
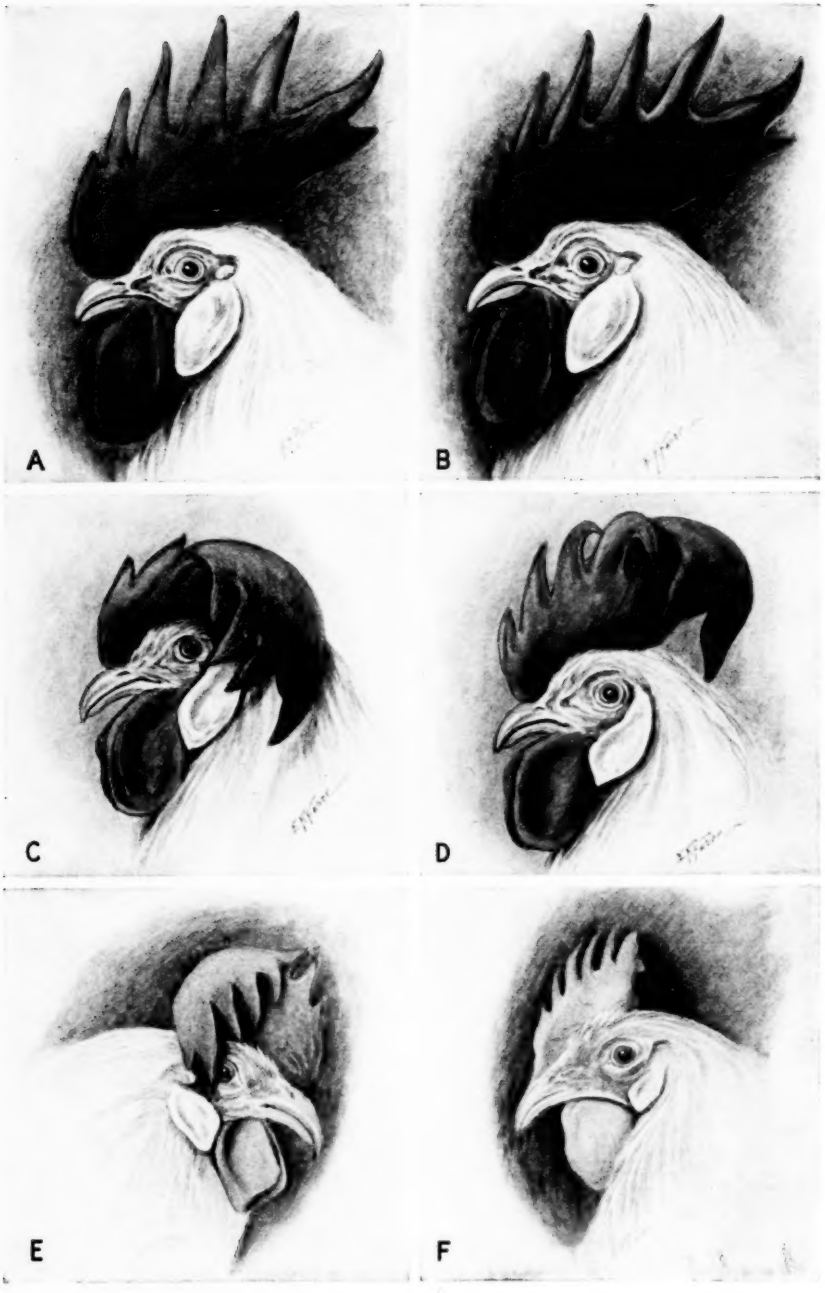


PLATE II



Consecutive injections were made in clockwise rotation through the 4 quadrants of the breast. Gangrene was produced in the combs of 5 cocks by application of a heavy elastic band. Sixteen birds were sacrificed for control.

Injections were continued for 30 days in all groups except the first; the fluid extract produced such massive sloughs that there was little or no absorption after the 14th day and the last animal was killed on the 25th.

Longitudinal and transverse sections were taken through digitations 6 and 7 of the comb and from brain (in some), aorta, heart, lungs (in some), spleen, kidney, testis (in some), stomach, liver and breast muscle, for histologic examination.

Results. GENERAL STATUS OF THE ANIMALS. 1. *Fluid extract of ergot:* There was marked loss of weight, the animals rapidly becoming extremely emaciated. Breast muscle was necrotic and the majority showed ulceration; 54% of this group died, one 5 days after injections were begun.

2. *Ergoklonin (normal concentration):* The condition of the animals at the end of the 30-day period seemed quite as good as at the outset; there was no weight loss. Muscle showed no induration or slough; no deaths.

3. *Ergoklonin (concentrated 2×):* The birds showed minor weight loss but were not emaciated. Breast muscle became indurated after about 8 days but did not ulcerate; no deaths.

4. *Ergoklonin (concentrated 4×):* Considerable weight loss was observed in all but 1, although not to the degree seen in Group 1; the animals appeared ill after the first week; 2 deaths, probably from upper respiratory infection.

5. *Ergonovine (twice daily):* Nutrition remained good and animals appeared quite healthy. No induration or necrosis of muscle occurred; no deaths.

6. *Ergonovine (4 times daily):* Same as Group 5 except for 1 sudden death immediately after injection on the 30th day, cause of which was not determined by autopsy.

CONDITION OF THE COMB. 1. *Fluidextract of ergot:* One animal remained free of gangrene, but showed unrelieved blanching and moderate atrophy of comb. Gangrene of digitations 5, 6 and 7,

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PLATE II.

A, Ergoklonin (normal concentration): Bluing reaction 1 hour after injection; cock had received 1.5 cc. intramuscularly twice daily during the previous 29 days (No. 164). *B*, Ergoklonin (normal concentration): Same animal 7 hours after injection which had produced the bluing reaction in *A;* there is complete restoration of the comb to a normal status (No. 164). *C*, Ergoklonin (concentrated 2×): Bluing and drooping of the comb 1 hour after injection on the 28th day of the experiment; cock had received 1.4 cc. of the concentrate intramuscularly twice daily during the previous 27 days (No. 140). *D*, Ergoklonin (concentrated 2×): Same animal 7 hours after injection which had produced the reaction shown in C; there is slight residual cyanosis and normal erectility is not restored (No. 140). *E*, Ergoklonin (concentrated 4×): Moderate atrophy and pallor after intramuscular injection of 1.8 cc. of the concentrate twice daily for 15 days (No. 112). *F*, Ergoklonin (concentrated 4×): Marked atrophy and pallor produced by intramuscular injection of 1.92 cc. of the concentrate twice daily for 29 days (No. 131).

involving the distal 2 to 4 mm., occurred in 2 but did not progress. There was advancement of the gangrene in all others, almost to the base of the digitations, accompanied by withering of the comb and wattles; in 2 animals, spontaneous amputation of digitations 6 and 7 occurred (Plate I, *C* and *D*).

2. *Ergoklonin (normal concentration):* Within 10 minutes after injection slight circumocular pallor appeared, followed by minor blanching of the root of the comb and wattles; in about 15 minutes the dorsal third of the comb was cyanotic and cold. Cyanosis spread ventralward over half or more of the comb during the next 15 minutes but in an hour had regressed considerably and at the time of the next injection the comb had resumed the original bright red color and warmness. No gangrene was observed in the group and combs maintained original size and erectility (Plate I, *A* and *B*).

3. *Ergoklonin (concentrated 2×):* The primary reaction to injection was similar to Group 2 but cyanosis of the dorsal third persisted to slight degree for 7 or 8 hours. There was considerable flaccidity of the comb in this group, most marked about 1 hour after injection and erectility was never quite regained before the next dose. Gangrene appeared in 4 birds, in 3 not progressing beyond the distal 2 or 3 mm. of digitations 6 and 7; 1 showed moderate advancement of the process 3 to 4 mm. farther, involving digitations 4 and 5 slightly (Plate II, *C* and *D*).

4. *Ergoklonin (concentrated 4×):* During the first week the reaction paralleled Group 3; thereafter a tendency toward continued pallor of the comb was noted with slight gangrene appearing in 4 of the animals which remained stationary, but there was moderate to marked atrophy of the comb, to lesser degree of the wattles (Plate II, *E* and *F*).

5. *Ergonovine (twice daily):* The primary reaction was similar to Group 2, more marked, however, and the cyanosis at the end of an hour was deeper, but there was complete regression within 7 hours. At the end of the 30-day period, the combs were entirely normal except for a tiny gangrenous patch, 1 mm. long, at the tip of digitation 7 in one bird. This appeared on the 17th day and did not progress.

6. *Ergonovine (4 times daily):* No essential differences were noted between this and Group 5 except that no gangrene appeared; normal color and temperature were not quite restored between injections during the day but resumed normal state between the evening and the first morning doses (Plate I, *E* and *F*).

7. *Mechanical pressure:* Immediate deep cyanosis followed application of a heavy elastic band between the root of the comb and the cleft between digitations 4 and 5; this proceeded to early gangrene in 1 day, moderately advanced in 3. The necrotic portion of the comb was more moist than is the gangrene of ergotism, but was otherwise the same.

Histologic Appearances. Regarding the mechanism of gan-

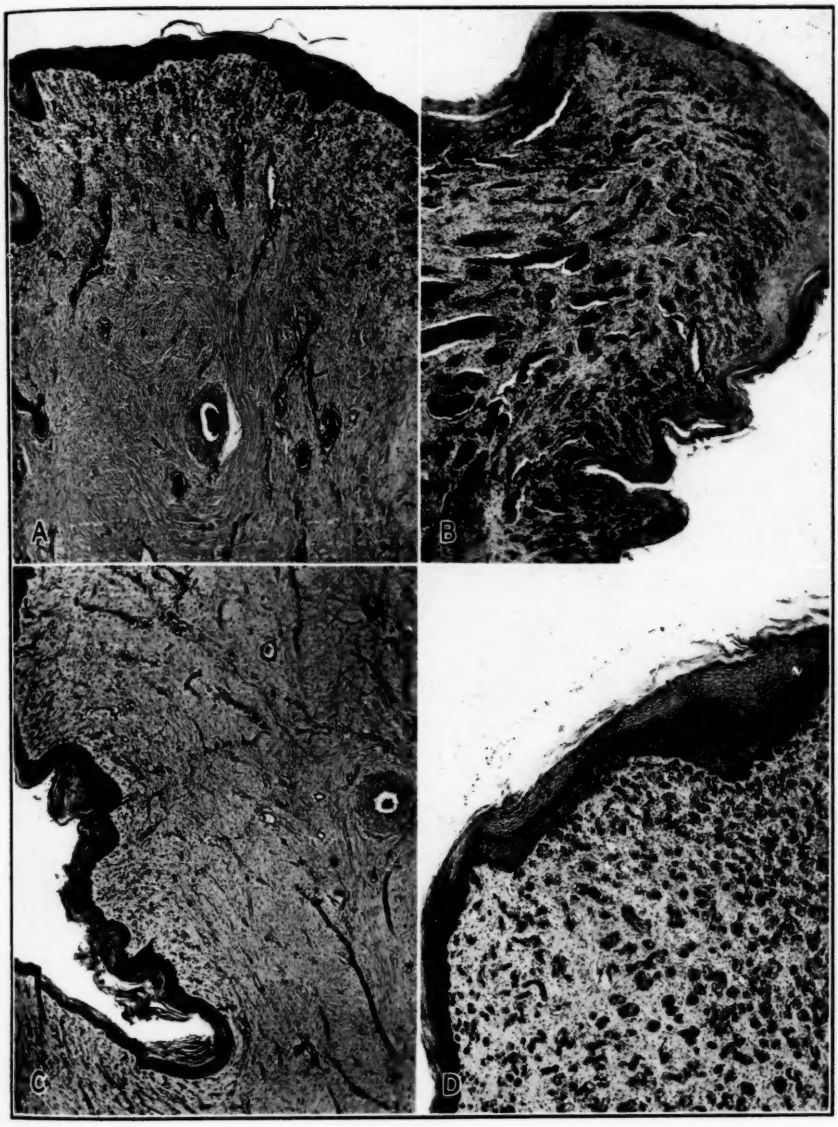

PLATE III.

(All photomicrographs magnified 69×.)

A, Normal control: Comb showing epidermis, cortical cavernous capillary bed and central loose connective tissue; note thick muscularis of central artery (No. 177). *B*, Mechanical gangrene of comb: There is necrosis of the epidermis; great dilatation of the capillary bed is accompanied by loss of endothelium and extensive thrombosis (No. 190). *C*, Ergonovine: Comb appears entirely normal, cock having been killed after resumption of normal color; animal had received 0.63 mg. of ergonovine intramuscularly twice daily during the previous 29 days (No. 167). *D*, Ergonovine: Comb of animal killed during the stage of cyanosis; capillary bed is dilated but endothelium is preserved and there is no thrombosis; epidermis is normal (No. 168).

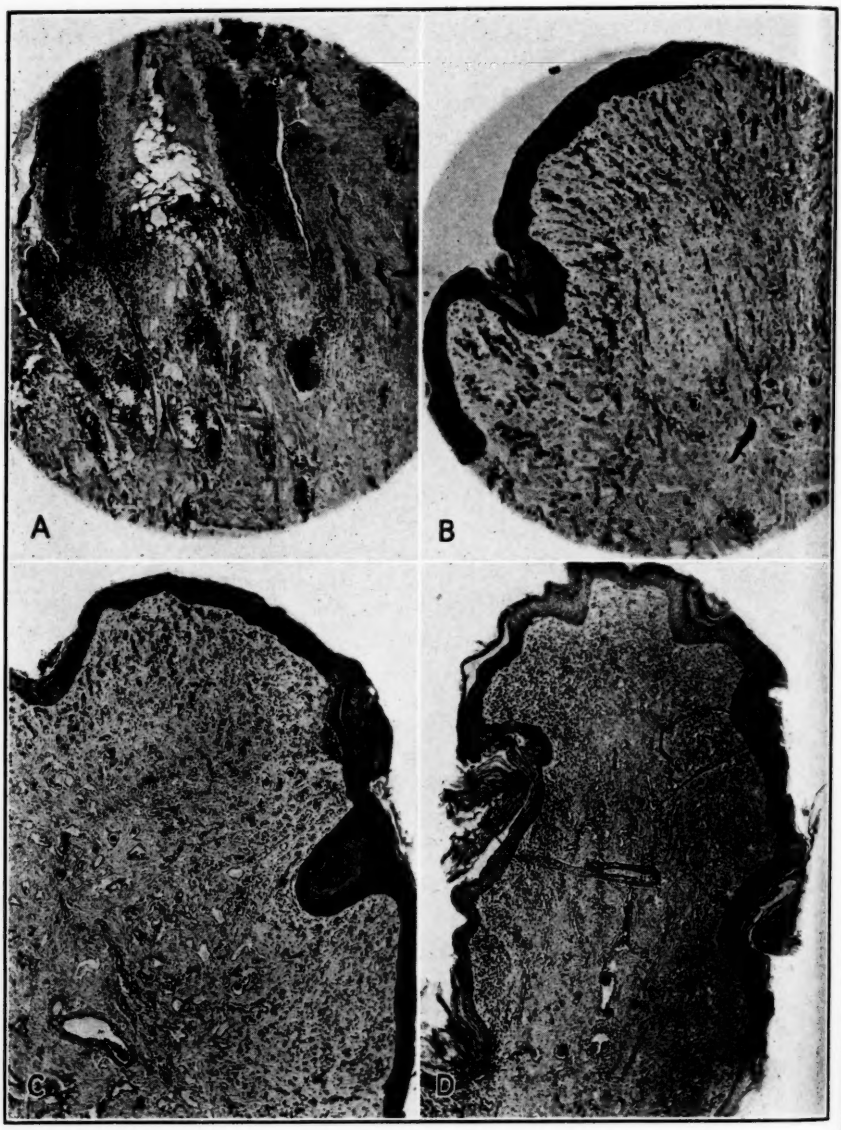

PLATE IV.

(All photomicrographs magnified 69×.)

A, Fluid extract of ergot: Comb at line of demarcation of gangrene showing dilatation and thrombosis of arteries and veins; cock had received 1 cc. twice daily for 17 days (No. 115). *B*, Ergoklonin (normal concentration): Histologic appearances are normal after intramuscular injection of 1.42 cc. twice daily for 29 days (No. 163). *C*, Ergoklonin (concentrated 2×): Shows only minor dilatation of the capillary bed; no necrosis after having received 1.06 cc. twice daily for 29 days (No. 139). *D*, Ergoklonin (concentrated 4×): There is atrophy and ischemia of the comb after receiving 1.92 cc. of the concentrate twice daily for 29 days (No. 131).

grene in the comb, the observations of Lewis are entirely substantiated. Primarily there is apparently an unrelieved arteriospasm with congestion, anoxemia and endothelial degeneration in the capillary beds, followed by stasis thrombosis therein and subsequent necrosis of the tissues. Propagation of thrombosis is followed by progress of the gangrene. Blood-vessels of the fowl present a considerably thicker medial muscularis than those of mammals, and cocks killed when the comb was cyanotic or blanched showed the arteries in a state of vigorous contraction, as evidenced by a relatively thicker wall in relation to the lumen, rugated elastica and more or less radial arrangement of intimal endothelium. It is perhaps for this reason that the cock's comb is unduly sensitive to the pharmacologic action of the ergot group. There was no evidence that the protracted administration of any of the drugs in this series produced permanent medial hypertrophy or arteriosclerosis. With the exception of the group receiving fluid extract of ergot, no visceral lesions analogous to changes in the comb appeared, save for ischemia in those animals killed during a period of generalized vasospasm. In the fluidextract group, 1 cock showed a small infarct of the myocardium and 3 presented liver degeneration with increase in interstitial tissue between the cords of liver cells; renal glomeruli were relatively ischemic as well. Essential changes in mechanically produced gangrene of the comb were the same as in ergotism.

Conclusions. While ergonovine and ergoklonin produce rapid and protracted contraction of the uterus, the coincident vasospasm (upon which the production of gangrene depends indirectly) is relatively fleeting. Vasospasm is comparatively unrelieved following administration of fluidextract of ergot, however, and gangrene of the cock's comb ensues. Even in the presence of moderately advanced gangrene of comb there is little or no visceral damage demonstrable.

One must realize that the dose of the drugs in these experiments is far in excess of that administered therapeutically. It is legitimate to state, then, that ergonovine and purified liquid preparations of ergot, standardized for their content of this alkaloid, may be used without fear of ergotism.

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ERGONOVINE VERSUS ERGOTAMINE AS A TERMINATOR OF MIGRAINE HEADACHES.*

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Confused thinking about migraine and disappointing results of treatment are due in part to a failure to define and to integrate the many factors involved. The ophthalmologist, the gynecologist or the psychoanalyst is apt to see the patient as a case of astigmatism, of dysmenorrhea or of mother fixation, and treating only that aspect, neither cures the patient nor does credit to his specialty.

Conditions Which Cause Seizures of Migraine.

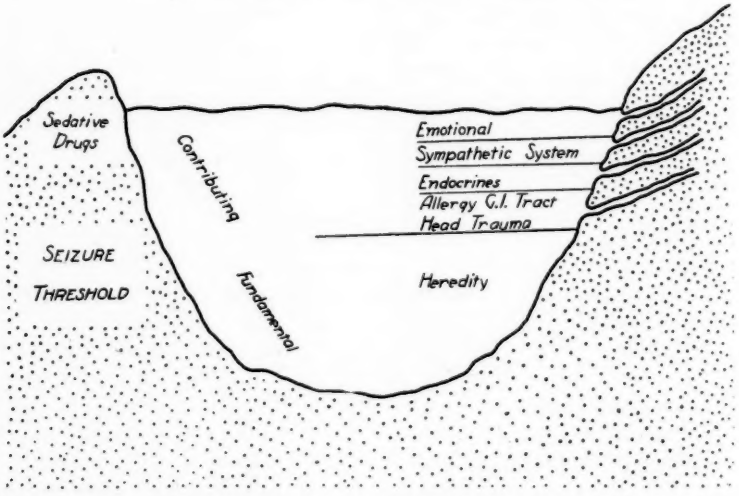

Fig. 1.—The various fundamental and contributory conditions which may cause seizures of migraine in the individual patient. A periodic increase of influences results in a periodic overflow of the reservoir; such overflow representing a migraine attack. Attempts at therapy should include the stopping of contributory factors and the elevation of the patient's threshold for pain.

Not only in any group of migraine patients, but also in each individual patient, multiple causes are, I believe, at work. In general, these are the same causes which produce epilepsy, but in different proportions. Many printed words can be saved by expressing the multiple factors in the form of a line picture. The conditions which combine to produce the symptom, migraine, may be represented as underground springs which feed a reservoir. When the waters

* Aid was received from the Josiah Macy, Jr., Foundation.

of the reservoir rise, as they periodically do, and overflow the banks, this represents a migraine attack. Whether overflow occurs will depend in part on the number and size of the feeding springs, and in part on the height of the restraining banks. The problem of the physician is to discover and, if possible, to block the springs and also to elevate the patients' threshold for pain.

The various causes of migraine, and their relative importance, not only differ from patient to patient, but also in the same individual from time to time. Later von Storch and I will attempt statistical analysis of the various causes encountered in our patients. For the present, without attempting to assign values, I show in the accompanying figure some of those factors which are considered of etiologic significance in migraine. This preliminary exposition is for the purpose of orientation and in order to place in its proper proportions what will be said about ergot.

Crude ergot in the treatment of migraine has had an occasional proponent. In 1898 Thomson[25] wrote "Ergot in full doses is superior to any other agent in arresting the headache," but whether because of ergot's histamine constituent or because of its instability, the drug has never held a recognized position on a shelf crowded with migraine remedies. In 1926 and later, several reports appeared in European journals favorable to the use of the alkaloid ergotamine tartrate. I began treatment of migraine with ergotamine tartrate 5 years ago, and since that time, my associates and I have administered the drug to 140 patients for the relief of an aggregate of thousands of headaches.[13,15] Injection of ergotamine tartrate terminates the headache of nine-tenths of our patients, a proportion also encountered by other authors, notably O'Sullivan[3,19] and Logan.[17]

Aside from the dramatic effect of ergotamine in the termination of headaches, the action seems to be specific for headaches of the migraine type.[16] Therefore the drug does more than increase the headache threshold—it temporarily blocks the inflow of waters which feeds the headache reservoir. On a subsequent occasion, however (perhaps even before the usual interval), the inflow resumes and the succeeding attack occurs. Ergot is not a "cure" for migraine. It is not even a means of preventing headaches, for injection of the frequent doses needed would be neither safe nor practical. Ergotamine affords speedy relief to the patient after the attack begins and an opening wedge to the investigator. Associates and I have reported certain laboratory studies of ergotamine tartrate.[21,22] The purpose of this paper is to record results obtained with another ergot alkaloid, ergonovine.

The isolation of a new and more active oxytocic alkaloid of ergot was announced during a short period of time from 4 different laboratories.[4,5,6,11,23,24] After some confusion over questions of priority and whether the substances were identical, the various workers agreed that they were.[12] The Council of Pharmacy and Chemistry

adopted for the new substance the name of "Ergonovine;" the empirical formula is $C_{19}H_{23}N_3O_2$. Proprietary names have been selected by the various pharmaceutical houses.

Methods. The names, amounts and manufacturers* of the medicines which are mentioned in this paper are listed below. The dosage used had to be suited to the individual, but the maximum amount was ordinarily 1 ampule given intravenously and 2 tablets taken hourly until headache was relieved or 8 tablets had been taken. In the case of ergoklonin liquid, a teaspoonful was given hourly until relieved or 4 doses taken. The ampules are for injection and the tablets and liquid for oral administration.

Ergotamine tartrate (gynergen) (Sandoz) a 1 cc. ampule contains 0.5 mg. and a tablet contains 1 mg.

The various preparations of ergonovine are:

Ergobasine tartrate (Basergin) (Sandoz), a 1 cc. ampule contains 0.2 mg. and a tablet contains 0.25 mg.

Neo-gynergen (Sandoz), a 1 cc. ampule contains 0.25 mg. ergotamine tartrate and 0.125 mg. ergonovine (ergobasine tartrate) and a tablet contains the same.

Ergoklonin (Wyeth), a 2 cc. ampule contains 0.4 mg. ergonovine and liquid for oral use contains 0.4 mg. per 4 cc.

Ergometrine (Burroughs-Wellcome), a 1 cc. ampule contains 0.5 mg. and tablet 0.5 mg.

Ergotrate (Eli Lilly), a 1 cc. ampule contains 0.2 mg. hydracrylate of ergonovine.

Patients were those attending the migraine clinic at this hospital or were private patients. Most of these had already received treatment with ergotamine tartrate, results of which in 120 patients have been published.[15]

Results. Observations of the clinical effect on patients extend over the past 2 years. Tabulation based on the total number of headaches treated would be unfairly weighed with successful results, since only those who were helped continued to take treatment. The first trial is usually prophetic of the usefulness of an ergot preparation. The therapeutic results include not only the effect on the existing headache, but also the patient's attitude towards the magic disappearance of his pain. Instead of being jubilant, some patients seem unimpressed and complain of some unpleasant symptom, which precludes continued use of the drug. Seemingly, subconsciously, they cling to their headaches. Ordinarily, only the results obtained from the initial administration of the drug were counted, but in those cases in which different preparations of ergonovine were used, or in which the severity of headaches varied markedly, an average result of the different trials was set down.

Seventy-eight different patients received treatment for migraine headache with one or more of the various preparations of ergonovine. The results are presented in Table 1, together with comparable data for 140 patients who received treatment with ergotamine.

Parenteral Administration. Fifty-four patients received injec-

* Each of these firms provided us with liberal supplies for clinical use, and in addition Sandoz Chemical Works and John Wyeth and Bro. contributed funds toward the laboratory expenses of the investigation.

tion of one of the ergonovine preparations during headache, 39% of these administrations resulted in complete cessation of the headache and other symptoms. In 40%, the headache was only partially relieved or was stopped, but later returned. In 17% headache was not affected, and in 4% it became worse. Patients who were relieved found the time interval between injection and the beginning of relief about the same as for ergotamine tartrate, namely 30 to 60 minutes. This is in contrast with the fact that ergonovine affects uterine contractions much more promptly than does ergotamine tartrate.

These results may be contrasted with those for ergotamine. In 140 cases in which von Storch or I have administered ergotamine parenterally, the headache was stopped completely in 89%, improved in 5% and not improved or became worse in 6%. Therefore ergonovine was less than half as effective as ergotamine in terminating headaches, though if complete failures are compared, ergonovine's showing was not so unfavorable, 21% of failures, against ergotamine's 6%.

Oral Administration. Information concerning the drugs taken by mouth is not so reliable, because the immediate effect was not witnessed by the author. The results (Table 1) probably err on the

TABLE 1.—EFFECT OF THE ADMINISTRATION OF ERGONOVINE AND OF ERGOTAMINE ON MIGRAINE HEADACHE.

Route.	Drug.	No. of patients.	Percentage. Well.	Improved.	Not improved.	Worse.
Parenteral . .	Ergonovine	54	39	40	17	4
	Ergotamine	140	89	5	4	2
Oral	Ergonovine	42	43	24	33	0
	Ergotamine	56	41	27	30	2

favorable side, because some patients who were not benefited by the injection of ergonovine did not take it by mouth, and because those who did, but were not benefited, were less likely to return for renewed supplies and to report results. Table 1 is more useful for the comparison of different drugs than for the comparison of routes of administration. The two ergot alkaloids yielded practically the same results when taken by mouth, a similarity not observed when the drugs were injected. The fact that ergotamine is absorbed with difficulty from the gastro-intestinal tract, and ergonovine is readily absorbed, probably accounts for the differences observed.

These results indicate that injection of ergonovine is less than half as effective as ergotamine tartrate in completely aborting migraine headaches. However, of migraine patients who are relieved by ergonovine, many prefer ergonovine to ergotamine, either, because they experience fewer gastric symptoms, or because relief may be had from the ingestion of the drug.

Occasionally, a patient whose headache is ordinarily relieved by

injection of ergotamine will have an unusually severe headache which ergotamine does not terminate. In such a desperate situation, I have repeatedly found that the intravenous injection of 2 cc. of the amidopyrine compound "cibalgine" would complete the relief.

Gastric Symptoms. Aside from welcome release from headache by means of ergot, an important question concerns the unpleasant symptoms which a patient may experience. Sensations of muscle soreness and of fatigue are certainly more common after ergotamine than after ergonovine. The most frequent symptoms are nausea and vomiting. Adair[1] and colleagues encountered vomiting "but rarely" in postpartum patients given 0.2 mg. ergonovine. My results with ergonovine and with ergotamine (including data for ergotamine reported by Lennox, von Storch and Solomon[16]) are shown in Table 2. Migraine patients who had nausea and vomiting

TABLE 2.—PROPORTION OF PATIENTS HAVING NAUSEA OR VOMITING AFTER ADMINISTRATION OF ERGOTAMINE OR ERGONOVINE.

Patient's headache.	Ergotamine tartrate I.V.			Ergonovine I.V. and P.O.		
	No. of cases.	Percentage having:		No. of cases.	Percentage having:	
		Nausea.	Vomiting.		Nausea.	Vomiting.
Without headache . .	38	47	18	21	24	4
Non-migraine . . .	46	56	37	18	50	11
Migraine	110	78	57	64	58	25
All cases	104	67	45	103	50	18

before the drug was given are not listed as positive, unless an increase of symptoms resulted.

Inspection of the table shows that patients having migraine headaches, vomited less than half as frequently after ergonovine, as after ergotamine. Since ergonovine is less than half as effective as ergotamine in terminating migraine headaches, the question arises whether ergotamine acts by inducing vomiting.

However, separate tabulation of those cases receiving ergonovine in which the effect, both on headache and on the gastric symptoms was clear cut, showed that patients who obtained complete relief from the use of ergonovine, had even less nausea and vomiting than those not relieved.

Headache.	No. of cases recorded.	Percentage experiencing:	
		Nausea.	Vomiting.
Completely relieved	31	45	31
No relief or worse	21	57	43

Effect on Blood Pressure. The principal fear on the part of clinicians in prescribing ergotamine tartrate is the possibility of arterial

constriction of peripheral vessels leading to occlusion. Such fears have been augmented by reports of gangrene, after the administration of ergotamine to patients with serious liver damage or with septic infection.[9,20,26] In the treatment of migraine patients, such fears have been without substantial grounds, either in our experience or that of others. Practically every one of the migraine patients coming under the care of my associates and myself in the past 5 years, including cases with essential hypertension and arteriosclerosis, have received ergotamine. Some have taken it for nearly 5 years, some require several ampules weekly, 2 elderly women with status migraine have each taken hundreds of injections; but we have never encountered more than transient symptoms of an inadequate peripheral circulation. Most writers agree that the injection of ergotamine tartrate causes a moderate, temporary increase in systolic and diastolic blood pressure. We have seen or heard of no cases in which ergotamine seemed to be the cause of a continued high level of blood pressure. However, judgment on the ultimate effects of ergot on the vascular system must await the accumulation of evidence over a period of many years.

Because the tonic action of ergonovine on the smooth muscle of the uterus is so prompt and prolonged, the effect of ergonovine on blood pressure requires careful examination. Adair and his associates[1] measured blood pressure in a "considerable number" of parturient women. Their data indicate an average rise of 5 mm. systolic and a fall of 3 mm. diastolic pressure. The time interval after injection was not given. On the other hand, Cushny[7] states that ergonovine causes increase of blood pressure.

My associates, Dr. Page Newbill, Hildegard Leonhardt, Doris Thaler, and I measured the blood pressure before and at short intervals for an hour after the intravenous administration of ergonovine in migrainous and other patients. These data, and similar information concerning ergotamine, are gathered in Table 3. The table records the average figures for the various groups; the blood

TABLE 3.—AVERAGE MAXIMUM INCREASE OF BLOOD PRESSURE AND DECREASE OF PULSE RATE FOLLOWING ADMINISTRATION OF VARIOUS DRUGS WHICH INFLUENCE MIGRAINE.

Drug.	No. of cases.	Systolic B.P.		Diastolic B.P.		Pulse rate.	
		Initial.	Increase.	Initial.	Increase.	Initial.	Decrease.
Ergotamine I.V. . . .	62	120	19	76	16	85	16
Ergonovine I.V. . . .	35	117	14	77	10	76	4
Ergonovine P.O.* . . .	23	118	6	78	7	74	6
Epinephrine S.C. . . .	14	126	25	84	7†	81	27‡

* Twelve cubic centimeters ergonovine (ergoklonin) given per os.
† Decrease.
‡ Increase.

pressure and pulse rate before the drug was administered, and afterwards the highest readings of the systolic and of the diastolic blood pressure, and the lowest pulse rate. The maximum systolic reading did not always coincide with the maximum diastolic.

Regarding blood pressures, ergotamine tartrate, when injected intravenously in 62 patients, resulted in an average maximum rise of 19 mm. systolic and of 16 mm. diastolic. This diastolic rise is the same as obtained by Freeman and Carmichael[8] in a group of 24 normal subjects, whereas our systolic rise is 6 mm. greater. Following intravenous injection of ergonovine, the average maximum increase of systolic pressure was 14 mm. and of diastolic pressure 10 mm., a smaller increase than occurred after ergotamine. Ergonovine (ergoklonin) taken by mouth caused relatively slight alterations, an increase of 6 mm. systolic and 7 mm. diastolic. The blood pressure changes experienced by 14 patients following subcutaneous injection of 0.1 mg. epinephrine are included for comparison. Ergotamine and ergonovine caused no significant change of pulse pressure, whereas the increase after epinephrine was great.

The distribution of the changes in systolic blood pressure readings is also of interest. An insignificant increase in systolic pressure (less than 11 mm.) occurred in 48% of patients after ergonovine and in 37% after ergotamine. An increase in systolic pressure between 11 and 20 mm. was noted in 40% of patients after ergonovine and in 29% after ergotamine. Increases of pressure exceeding 20 mm. occurred in 12% of patients after ergonovine and in 34% after ergotamine. The changes in blood pressure may vary greatly from time to time. For example, Mrs. W. had the following maximum increases in systolic and diastolic pressures, respectively: after neogynergen 6 and 26; after ergonovine on three occasions 22 and 26; 65 and 65; 3 and 0.

Is the increase in systolic blood pressure dependent on the initial pressure? Tabulation of this point for patients receiving intravenous injections of ergotamine and ergonovine showed that subjects with an initial pressure above 130 had a relatively small increase of pressure. Two patients, who received ergotamine intravenously, had initial systolic pressures of 195 and 230 mm. respectively. The maximum readings after the injection were respectively, 7 and 4 mm. lower. Meakins[18] and associates have used ergotamine in the treatment of hypertension.

Is the increase in blood pressure a prerequisite for relief of headache? Tabulation indicated the lack of any positive correlation. The increase in systolic pressure was 13 mm. for patients who were relieved, 17 mm. for those not relieved and 19 mm. for those without headache when the test was made.

Pulse Rate. Changes in pulse rate seem of little interest to the clinician, but are of moment in attempted explanations of the mechanism of migraine attacks and of their relief by the ergot

alkaloids. The decrease in pulse rate after administration of ergotamine is well recognized, and has been generally attributed to a paralyzing effect on those sympathetic nerves which increase the rate of the heart. Youmans and associates,[28] however, believe bradycardia is due to vagus stimulation, as the effect in human subjects is abolished by atropine.

The data in Table 3 indicate that the intravenous injection of ergotamine was followed by a pronounced fall in pulse rate (in 62 patients an average maximum fall of 16 beats). The average maximum fall after the injection of ergonovine was only 4 beats and after its ingestion 6 beats. After epinephrine injections, the average maximum increase was 25 beats.

Tabulation of the distribution of changes showed a decrease of less than 10 beats in 76% of cases receiving ergonovine injections against 27% receiving ergotamine. There was a bradycardia of more than 20 beats in no case receiving ergonovine and in 30% of cases receiving ergotamine.

Youmans and associates[27] believe the effect of ergotamine is more pronounced when the sympathetic nervous system had been stimulated by epinephrine. Is the degree of bradycardia in our observations dependent on the initial pulse rate? And, if so, can the more marked bradycardia in the group receiving ergotamine be due to a larger number of patients with a high initial pulse rate? Tabulation bearing on this point follows.

	Ergotamine.		Ergonovine.	
Initial pulse rate.	No. of cases.	Average decrease of pulse rate.	No. of cases.	Average decrease of pulse rate.
Less than 80	23	9	25	2
80 to 99	21	19	13	9
100 and over	12	29	0	0

True, bradycardia is greater, at least in absolute numbers, when the initial pulse rate is high. Also it happened that only patients who were to receive ergotamine had an initial pulse rate above 100. However, these circumstances but partially explain the differences in the average maximum decrease for the two groups. Even those patients whose initial pulse rate was below 100, had less bradycardia after injection of ergonovine, than after injection of ergotamine.

Can improvement in headache be correlated with the presence of bradycardia? There is some such correlation, both in point of time after injection and statistically. Subjects without headache had a decrease of 13 beats. Those who obtained complete relief from their headache had a greater fall of pulse rate (12 beats) than patients not relieved (7 beats). However, the smaller decrease in unrelieved patients was due, in part, to the fact that these had an average initial pulse rate 6 beats slower than patients who were relieved.

Other Circulatory Symptoms. In addition to changes in blood pressure and pulse rate, occasionally patients complained of symp-

toms which have to do with circulation. Transitory tingling of the fingers and congested appearance of the hands have been encountered after ergonovine, as well as after ergotamine injections, though not, I think, so frequently. The same is true of precordial pains. Complaints of precordial pains coincided in time with the maximum changes in blood pressure, but were not confined to those occasions in which pronounced increases in pressure occurred.

One very unusual patient was Mrs. T., who had a history of chronic headache of a questionable migraine type, and who was subject to attacks of the following symptoms: severe pain in the left groin, left hemiparesis and parasthesia of central origin, followed by an elevated blood pressure, by precordial pain and cardiac asthma. In one of these attacks the region of the left femoral artery had been explored with the expectation of finding an embolus —but instead the artery was constricted. We believed she had paroxysmal contraction of the arteries of the brain and leg. I gave her ergonovine intravenously as a diagnostic test of her headache. Three minutes after the injection she complained of paræsthesia of the left side of the body and face. Six minutes later she had precordial pain and the blood pressure was increased by 17 mm. systolic and 20 mm. diastolic. After an hour, the symptoms continuing, the patient had one of her attacks of cardiac asthma which was relieved by inhalation of 10% of carbon dioxide and 90% oxygen, a mixture which is most effective in dilating arterioles of the brain. During the attack the affected left limb felt colder than the right and pulsations of its arteries could not be felt. I was unable to secure blood from the internal jugular vein. In this patient subject to attacks of arterial spasm, an attack was precipitated by an injection of ergonovine.

Comment. Ergotamine and ergonovine in their therapeutic action on migraine headaches and also in their effect on blood pressure and heart rate act in the same direction. Differences between them in the respects mentioned are quantitative and not qualitative. In another communication Leonhardt and I[14] have shown that ergotamine and ergonovine, both cause increase in the flow of blood through the arm and an increased concentration of both arterial and venous blood. The changes in blood concentration (like the relief of pain, and the changes in blood pressure and in heart rate) were less pronounced following the administration of ergonovine. The termination of headaches by ergot alkaloids cannot be explained directly by anyone of these circulatory changes, for similar or greater changes in blood pressure, in blood flow, in blood concentration and in heart rate can be brought about by other agencies which do not stop migraine headaches. Nevertheless, these various alterations acting together and in combination with other, as yet unstudied, influences may eventually be explanatory of the mechanism of migraine and of its relief.

These present observations indicate that the ergot alkaloids do not help headache by virtue of a paralyzing action on the sympathetic nervous system, thereby either permitting the dilatation of spastic cerebral vessels or the anesthetizing of pain-carrying sensory nerve fibers. Rather ergotamine and ergonovine seem to be stimulating, causing a "tightening up" of the blood vascular system. Of particular value are the observations of Graham and Wolff[10] of a decreased amplitude of the pulsations of the temporal arteries at the time migraine patients were relieved of headaches by means of ergotamine.

The evidence that I have presented indicates that the oxytocic principle in ergot is not the principle which helps migraine headaches. Rather, the helpfulness of ergot seems to reside in the fraction which effects the contraction of arteries and the depression of the heart rate.

Ergonovine seems to have a distinct advantage over ergotamine in the treatment of puerperal states where a maximal effect on the uterus and a minimal effect on the arteries is desired. Probably, the specific and dramatic influence of ergot on migraine headaches cannot be secured without that fraction of ergot which influences the tone of arteries. Because migraine is a chronic condition persisting in many patients throughout life, and because those whose lives have been made livable by ergotamine are loathe to give it up on the mere suspicion of possible harm lurking in the dim future, there is need of intensive study of the effect of ergot alkaloids on the morphology and the physiology of arteries. In the Middle Ages epidemics of St. Anthony's fire from the consumption of grain spoiled by ergot had a convulsive and a gangrenous form.[2] Was the appearance of gangrenous ergotism in any way influenced by predisposition from race or from circumstances? What migraine patients, if any, should be refused the help of ergot alkaloids? What are the criteria for stopping ergot therapy once it is started? We, as yet, do not know the answer to these questions.

Each patient with migraine must be treated as an individual. There are tractable and intractable headaches. There is a powerful migraine pain killer (ergotamine) and one which is relatively weak (ergonovine). An elephant gun should not be trained on a rabbit and, if ergonovine proves effective, there is no need to prescribe ergotamine. Patients who find ergonovine effective usually prefer it, either because gastro-intestinal symptoms are not so pronounced or because relief follows oral administration. Ergotamine does not seem to have strong action as an abortifacient. Several migraine patients have continued to use it in pregnancy without ill effect. Ergonovine, on the other hand, should not be used during pregnancy.

In a disorder so stubborn as migraine and in dealing with patients who are so hard to hold, the more weapons the physician has the

better. Though far from being as effective as ergotamine, ergonovine can be useful in special situations. Ergotamine, ergonovine and non-habit forming sedative drugs should be prescribed in accordance with the needs of the individual. No drug, no matter how gratefully received, should be allowed to dull the physician's interest in finding, and if possible, removing the causes of the migraine.

Conclusions. Ergonovine has been used in 78 patients suffering from an attack of migraine headache. The injection of ergonovine terminated headache in 37% against 89% of patients receiving injection of ergotamine tartrate. Ergonovine brought partial or temporary relief to an additional 40% of the patients. The proportion not helped at all was 21% after ergonovine and 6% after ergotamine.

Ergonovine taken by mouth, while less effective than when injected, is relatively more effective than ergotamine tartrate taken by mouth.

Ergonovine causes slight increase of systolic and of diastolic blood pressure and a slight decrease in pulse rate, the average change being only about half the alteration observed following administration of ergotamine tartrate. The specific usefulness of ergotamine and ergonovine in the successful termination of migraine headaches is not related to their oxytocic action, but probably bears a relationship to the action of the alkaloids on the blood vascular system.

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DIAZOMETHANE POISONING.

First Clinical Case Report.

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So far as we are aware this constitutes the first clinical report of poisoning from diazomethane. References to the extreme toxicity of the gas and the symptoms produced by it have been confined almost exclusively to brief statements in the chemical literature. In view of the increasing use of diazomethane it would seem desirable to direct attention to the hazards of exposure to this reagent and to report one case of poisoning from it which has come under our observation.

Under ordinary conditions diazomethane is a gas, easily soluble in benzene or ether. Dissolved in these solvents it has proved to be a valuable reagent in the synthesis of organic compounds since it yields products of methylation quantitatively at room temperatures and without the assistance of other reagents. Owing to the expense in preparation, diazomethane has apparently not found many commercial applications. However, as a laboratory reagent the use of this compound has increased during the past few years to such an extent that methods for its preparation have been included in recent elementary manuals of organic chemistry.

Case Report. The patient is a male, aged 27, and a graduate student in organic chemistry. In the course of his laboratory work he elected to prepare trimethylbarbituric acid by allowing diazomethane to react with barbituric acid. The diazomethane was prepared by adding a concentrated solution of potassium hydroxide to nitrosomethyl urea and collecting the gas, CH_2N_2, in ether according to the procedure described by Arndt.† The ether solution containing the diazomethane was added directly with gentle stirring to barbituric acid at room temperature and 1, 3, 5–trimethylbarbituric acid was precipitated and nitrogen evolved.‡ Since diazomethane

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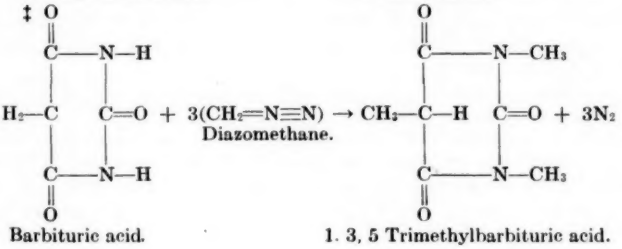
† $CH_3N(NO)CONH_2 + KOH \rightarrow CH_2N_2 + KCNO + 2H_2O$.
Methyl nitroso urea. Diazomethane.

‡



Barbituric acid. 1. 3, 5 Trimethylbarbituric acid.

is very volatile, the evolved nitrogen undoubtedly entrained some diazomethane.

Our patient neglected to conduct any of these procedures under a hood. While he may have inhaled some of the diazomethane while preparing the ether solution, nevertheless, it was while he was stirring the reagent into the barbituric acid that he suddenly became choked, dyspneic, and developed a violent, non-productive cough. The patient went to his home, where this attack continued for 3½ hours and gradually subsided. For the next 2 days he had paroxysms of dyspnea and coughing which recurred without any apparent reason. On the third day after exposure he developed a particularly violent paroxysm of coughing and orthopnea. Administration of ephedrine by his family physician afforded little relief.

During this time the patient was unable to retain food. Ingestion of food produced distention which he claimed interfered with his breathing and caused him to vomit. He also developed soreness of the abdominal muscles which he attributed to the labored breathing and retching.

On the sixth day after exposure to diazomethane the patient was admitted to this hospital in very grave condition. He had, according to report, neither slept nor eaten for 4 days. He was cyanotic, orthopneic, cold and dripping with sweat. The pulse was feeble and the rate was 132 per minute. The patient's chest lacked somewhat in resonance, and scattered throughout it were numerous musical and bubbling râles suggestive of pulmonary edema. Heart sounds were hardly audible. Following repeated injections of adrenalin and opiates the patient's condition improved greatly during the following day.

At this time the cough became productive of a thin, watery sputum which contained eosinophils, squamous epithelium, alveolar cells, Charcot-Leyden crystals and numerous bacteria. The blood count on admission was as follows: erythrocytes, 4.5 millions per c.mm.; hemoglobin, 14.2 gm. per 100 ml.; leukocytes, 10,800 per c.mm.; and a differential count of 76% neutrophil cells, 10% lymphocytes, 10% monocytes and 4% eosinophils. A week later the leukocyte count was decreased to 5800 and the differential count was essentially the same with 5% eosinophils present. The urinalyses on admission revealed a moderate albuminuria which became decreased to a barely perceptible amount without the following week. On spectroscopic examination of the blood only the bands of oxyhemoglobin were observed. Analyses of the blood and blood serum for urea nitrogen, sugar, chloride, CO_2, uric acid, cholesterol and bilirubin yielded concentrations within the normal range of values for these respective components.

On the day after admission a roentgenogram of the chest showed unusual prominence of the trunk shadows. A film made a week later revealed an unusual degree of hyperventilation of the lungs and a corresponding increase in the prominence of the trunk shadows.

An electrocardiographic tracing revealed a slurring of the *QRS* complex and a low *T* wave in Lead I. The pulse rate after the first 3 days following admission was between 90 and 100 per minute and the temperature which had been slightly elevated fell to a normal level.

The possibility was considered that poisoning with diazomethane might be related to the liberation of methyl alcohol. No disturbances in vision, however, were noted and the eyegrounds remained normal throughout the period of hospitalization.

The patient's condition in the hospital gradually improved so that within 2 weeks after the accident he became entirely free from attacks of dyspnea and coughing and after another week was discharged from the hospital. Repeated physical examinations of the heart and lungs during the week before discharge yielded essentially normal findings. The patient has moved to a distant locality and no recent follow-up examination has

been obtained. However, 4 months after his exposure to diazomethane he reported that there had been no recurrence of symptoms.

Comment. Diazomethane was discovered in 1894 by Pechmann[10a] who described it as being extremely poisonous, causing air hunger and chest pains. In a later article[10b] in 1895 he stated that he had been delayed in making further experiments on the compound owing to the poisonous effect that the gas had produced on him.

Corroborating Pechmann's observations, Bamberger and Renauld[3] in 1895 reported that they also had experienced toxic effects in experimenting with the gas and that their symptoms were essentially dizziness and tinnitus aurium.

In addition to these symptoms, Gottstein, Schlossmann and Teleky[6] reported that diazomethane produced denudation of the skin and mucous membranes. These authors claimed that the action of diazomethane was similar to that of dimethyl sulphate. Loring[8] also reported that the vapors from the ether solution of the gas were very irritating to the skin and rendered the fingers so tender that it was difficult to pick up a pin.

Arndt and Amende[2] in 1930 reported that 2 individuals were affected by the slightest traces of the gas, developing chest pains, fever and severe asthmatic symptoms about 5 hours after exposure to the gas. Arndt[1] described diazomethane as being "an especially insidious poison." He stated that "a person may work with it carelessly for some time without noticing effects. This leads, however, to a supersensitivity so that it is almost impossible to work even carefully with diazomethane without being subjected to attacks of asthma and fever."

The toxicity of diazomethane has been attributed by Flury and Zernik[5] to the intracellular formation of formaldehyde. Diazomethane reacts slowly with water to form methyl alcohol and liberate nitrogen.* Formaldehyde, in turn, is formed by the oxidation of methyl alcohol. The possibilities of liberation *in vivo* of methyl alcohol or of the reaction of diazomethane with carboxylic compounds to form toxic methyl esters may be considered;† on the other hand, the deleterious effects of diazomethane may be primarily due to the strongly irritant action of the gas on the respiratory system.

In addition to the toxicity of diazomethane, the explosive nature of this compound represents another hazard. Staudinger and Kupfer[11] reported that either in the gaseous or liquid state diazomethane exploded with flashes. Even at −80° C. Steacie[12] found that liquid diazomethane detonated. Several other investigators[4,7,9] have also directed attention to the explosive nature of this compound. It has been the general experience, however, that explosions

* $CH_2N_2 + H_2O \rightarrow CH_3OH + N_2$.
† $RCOOH + CH_2N_2 \rightarrow RCOOCH_3 + N_2$

do not occur when diazomethane is prepared and contained in solvents such as ether or benzene.

Animal Exposure to Diazomethane. Very little has been published on the toxicity of diazomethane for animals. Flury and Zernik[5] reported that an exposure of cats for 10 minutes to the gas in a concentration of 0.3 mg. per liter (about 175 parts per million) was followed within 3 days by death. The lungs of the cats showed hemorrhage, emphysema and edema.

To study its effect on animals, we attempted to secure a known low concentration of diazomethane mixed with air alone and free from volatile organic solvents. In accordance with the observations of others, however, we found mixtures of diazomethane with air alone to be violently explosive. The diazomethane in the experiments reported by Flury and Zernik was dispersed from a 2% solution of the gas in ether. Our experiments would indicate that this is probably a safer method of testing the toxicity of the gas.

In one of our experiments 2 cc. of 50% potassium hydroxide solution was poured over approximately 0.2 gm. of nitrosomethyl urea in the bottom of a 5-liter desiccator with an outlet open to the air. A guinea pig had previously been placed on a platform in the desiccator. After the introduction of the alkali, the guinea pig immediately began to strike its nose with its forepaws and to experience difficulty in breathing. Typically labored, asthmatic type of respiration ensued. After 25 minutes in the desiccator the pig was returned to its cage where it was found dead an hour later. Autopsy revealed inflated lungs from which on section edematous fluid oozed out. Histologic sections of the lungs showed a marked precipitable edema in the alveoli and bronchioles without appreciable congestion or swelling of the alveolar epithelium.

The pulmonary symptoms observed in diazomethane poisoning may be explained either on the basis of a true allergic sensitivity after repeated exposure to the gas, and particularly in individuals of allergic heredity; or on the basis of a powerful irritant action of the gas on the mucous membranes of the lungs. To support the former possibility is the statement by Arndt that individuals who had first handled the gas with relative impunity later experienced symptoms on even the slightest exposure. In the patient here reported a clear-cut history of asthma was obtained from his father and the patient himself reported that at times he had suffered mildly from hay fever. The only explanation, however, for the pulmonary lesions that we observed in the guinea pig after a primary exposure to the gas would appear to be that of a direct irritant action.

Summary. A case of poisoning by diazomethane is reported and attention is directed to the dangers of exposure to this gas.

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ACQUIRED SENSITIVITY TO CINCHOPHEN.

A Report of Six Cases and a Review.

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Clinicians know that thousands of people are able to take cinchophen (phenylcinchonic acid) and its compounds under a variety of conditions and over long periods of time, without apparent illness or injury. White[29] has estimated the consumption within the United States to be about 90,000 pounds yearly. Considering this widespread use, minor disturbances have occurred in only a small percentage of persons who use it, and only a fraction of 1% ever come to a fatal end as far as actually reported cases are concerned.

However, despite all the testimony as to the apparent harmlessness of cinchophen, the frequency of reports of toxic cirrhosis definitely attributed to its use are increasing rapidly. Many unreported cases have been discussed with physicians throughout this country, and several pharmacists have reported skin rashes after the use of this drug. The reason why more cases have not been reported will be explained later.

In this review, an effort will be made to demonstrate some striking examples of an acquired sensitivity, or susceptibility, to cinchophen and its compounds. Case reports will be presented which illustrate in a dramatic way reactions which followed immediately upon readministration of this drug or its derivatives. No evidence of toxicity, however, had occurred upon the first administration, even of large doses and over long periods of time. The apparent manifestations of cinchophen poisoning fall, in general, into several well-defined groups. In this report, and the 6 new cases, two groups are studied: (1) Cutaneous group of 10 cases with 2 deaths; (2) hepatic group of 22 cases with 12 deaths.

The mechanism by which one acquires a sensitivity from nonprotein substances such as cinchophen is not understood. This problem has been investigated by Landsteiner,[9] who was able to combine many of these substances with homologous animal sera and thus create compound proteins which have an immunologic activity comparable to a foreign serum. Antibodies have not been demonstrated, but Landsteiner[10] and others believe that an antigen

antibody mechanism explains drug hypersensitivity, though it has not been proven.

Acquired sensitivity, or the appearance of toxic symptoms when cinchophen compounds were given in courses or intermittently, has been observed and reported by Weir and Comfort,[27] Bloch and Rosenberg,[2] Quick,[18] Davis,[3] Short and Bauer,[24] Palmer and Woodall,[14] Fink,[5] and others. Many cases appeared to show idiopathic or non-acquired sensitiveness, but the previous use of the drug could not be ruled out because of the large number of compounds on the market under different names, all containing cinchophen in varying percentages.

According to Hench,[7] it is a constituent of over 500 remedies advertised in American literature as cures for rheumatism, or as uric acid solvents. The best known of these preparations are atophan and tolysin. Previous exposure, therefore, could have taken place without the knowledge of the patient; he might thus have become sensitized shortly after the first administration of the substance.

We have been impressed by this phenomenon, that although an individual does not show apparent toxic symptoms from cinchophen, damage may have occurred which may be accentuated by the second or third dose later on, even after several months or years. Willcox[30] first directed attention to the time factor which varies in length between the use of the drug and the first appearance of symptoms. The latter have frequently appeared weeks or months after the discontinuance of cinchophen, thus resembling the delayed effect seen in chloroform poisoning. It is also a common observation that a drug may be well tolerated for many weeks or longer, and then for some unknown reason the individual becomes receptive to its sensitizing action, and evidences of toxicity occur. Some allergists term this the refractory or delayed period of sensitization. This period may last for years for some, and days or weeks for others. This might explain why certain patients were noted who took cinchophen in a wide range of dosage at one time without symptoms, and later took the same amount or even a smaller dose, and became toxic. This theory in the future may lead to some interesting discoveries.

Lambert[8] remarked some years ago that one reason that acute yellow atrophy of the liver was much less often diagnosed, was that in the beginning it was not of the stormy type which physician had been taught to expect. Apparently the universal teaching in medical schools had been to diagnose all degrees of jaundice most often as the catarrhal type.

This observation may help to clarify the obscurities of cinchophen poisoning and explain the infrequency of its diagnosis throughout the country. The relationship between cinchophen and toxic cirrhosis has not been understood until recent years, even in the

presence of jaundice, and toxic cirrhosis without jaundice has not been appreciated at all. Most of the cases so far reported have come from large medical centers and it is unreasonable to suppose that they did not occur elsewhere.

The present review of acquired sensitivity to cinchophen was made after an inquiry into the records of most of the large hospitals in New York. A study was made of the deaths from liver disease in which autopsy reports were obtained, and of other fatal cases with obvious liver disease on which autopsies were not performed. This study did not yield much information as to the relationship between drugs and death from failure of liver function for several reasons: 1, Because of the lack of an accurate history of the patient's use of any drug; and 2, because of the lack of knowledge on the part of the attending physician that cinchophen compounds do cause deaths. Many autopsy reports were obtained with the diagnosis of acute yellow atrophy of unknown cause, while on the cases on which autopsies were not performed, several diagnoses were made, such as cirrhosis, acute yellow atrophy, acute hepatitis, acute catarrhal jaundice, and carcinoma. Several clinical histories were studied in which the patient died in a comatose state shortly after admission to the hospital. The necropsy report was usually acute yellow atrophy of unknown cause. These cases could not be included because of the lack of a proper history. Only in rare instances was a history obtained of the previous use of any drug, and the time factor which may elapse between the use of cinchophen and the appearance of symptoms, could be easily overlooked. All of this confusion, vagueness of symptoms, and lack of knowledge that cinchophen was toxic, explain to a certain degree the scarcity of reports of fatalities from the use of this drug.

In studying the reports of cinchophen poisoning as seen in humans, we cannot escape the conclusion that there must be conditions beyond control. The question has arisen, is the toxicity of cinchophen and its compounds limited to human beings? Reproduction of cinchophen toxicity in animals has not been accomplished to the complete satisfaction of all observers; in general, the results have been negative.

Many clinicians are unanimous in their belief that cinchophen compounds are definitely toxic to the liver, but how this is brought about is a mystery. Many theories have been brought forth which will not be discussed here. Several contend that allergy offers a satisfactory explanation, while others contend that the abnormal susceptibility theory is most rational. The proponents of the latter theory believe that cinchophen in the presence of certain predisposing conditions may sensitize or otherwise damage liver cells in such a way as to produce yellow atrophy. Among these predisposing conditions mentioned have been chronic infectious biliary tract disease, cirrhosis, pregnancy, chronic alcoholism, nephritis, low-carbohydrate diets, and surgical procedures.

Review of Cases. The accompanying table presents a brief analysis of 32 cases, including 6 reported by the author, all of which appear to illustrate the phenomenon of acquired sensitivity, or susceptibility of cinchophen (phenylcinchonic acid) and its compounds.

Summary. 1. Thirty-two cases of cinchophen poisoning are reported including 6 by the author, which appear to illustrate the

TABLE 1.—CASES OF CINCHOPHEN POISONING.

Cutaneous Group.

Case No.	Reference.	Drug and dose.	Total dose.	Symptomatology.	Result.
1	Maranon,[12] 1914	A. at irreg. intervals	Unknown	No symp. during this treatment	Recovered.
		A. at later date	Unknown (small)	Itching, chills, fever depression, eruption on neck and arms	
2	Maranon,[13] 1914	A. irreg.	Unknown	No symps. during first treatment	Recovered.
		A. at later date	Unknown, said to be small	Itching, chills, fever, rash	
3	Reichle,[21] 1929	C. on and off 5 or 6 times daily for several years	Unknown	No symps. during this period	Autopsy: Liver weighed 1950 gm. Spleen enlarged; yellow atrophy present.
		C. 80 tablets in 1 mo.; 40 tablets of oxyliodide 1 mo. and C.	Probably 400 gr. 40 gr. 60 gr.	Jaundice with recovery Fever, diarrhea, nausea, vomiting, bleeding from nose and gums, skin rash and death in coma	
4	Barron,[1] 1924	C. gr. 15 at irreg. intervals	Probably 200 gr.	No symps. over long period, then collapse for ½ hr. cyanosis; recovery	Recovered.
		C. 2 tablets 3 mos. later	10 gr.	Collapse again, pink rash appeared on arms, face and chin	
5	Davis,[3] 1932 (Case 1)	N. 45 gr. daily for 10 days	505 gr.	No symptoms	
		N.	30 gr.	Rash on skin and rise in temp.	Recovered when drug was stopped.
6	Davis,[3] 1932 (Case 2)	C. over 1 mo.	1200 gr.	No symps. except nausea at the end of this time	Recovered when drug was stopped.
		N. 2 mos.	1800 gr.	Urticaria after 1 month later,	Recovered when drug
		N.	10 gr.	severe urticaria	was stopped.
		N.	5 gr.	One week later, rash developed	
7	Short and Bauer,[24] 1933	E. 30 gr. daily for 6 mos.	5400 gr.	No symptoms	Recovered.
		oxyliodide later	69 gr.	No symptoms	Patient reacted with increasing sensitivity.
		oxyliodide 3 mos. later	3 gr.	Chills, fever, itching and severe urticaria	
			Farastin 7.5 gr.	7.5 gr. cyanosis and urticaria	
		C.		Generalized urticaria	
8	McVicar and Weir,[12] 1929	A. intermittently for 1 year	Unknown	No symps. until about 12th month after beginning drug. Itching, nausea, vomiting, which cleared up. Later erythema, vomiting edema, death	Autopsy: Liver presented gross, and histologic evidence of g. b., bile duct and panc. dis.
9	Westfall,[26] 1937	C., dose unknown	Unknown	No symps. at first. Later g.-i. symps., urticaria. Acquired sensitivity	Recovered.
10	Sugg, 1935 (Case 1)	A. 5 gr. t.i.d.	200 gr. 1933	No symptoms	Recovery after drug was stopped. Acquired sensitivity did not develop until 3rd year.
		A. 5 gr. t.i.d.	200 gr. 1934	No symptoms	
		A.	315 gr. 1935	No symptoms	
		A. gr. 10 for 2 days	20 gr. later	Generalized itching and rash over body	

A = Atophan. C = Cinchophen. E = Eucophen. F = Farastin. N = Neocinchophen T = Tolysin.

TABLE 1.—*Continued*

Hepatic Group.

Case No.	Reference.	Drug and dose.	Total dose.	Symptomatology.	Result.
11	deRezende[22] 1927	A. 5 gr. caps. t.i.d. 3 to 4 wks.	270 gr.	No symptoms	
		A. taken at later date	Unknown	Jaundice, duration 1 mo.	Recovered.
12	Rake,[19] 1927	A. indef. period	1500 gr.	No symps. for a long period. Then ac. abd. pain and jaundice	Autopsy: Liver weighed 1150 gm.
		A. gr. 10 over 2 days	10 gr.	Diag: Gallstones. Later diarrhea and vomiting recurred. Exploration, no gallstones found. Death 3 days later	Necrosis and regeneration.
13	Glover,[6] 1926	Atophanyl. Occasional intravenous injection	38.5 cc.	No app. di. arose until last series of treatments when there was evidence of liver damage	Recovered.
14	Loewenthal, Mackay, and Lowe,[11] 1928	A., 1.5 gm. daily for 6 mos.	3600 gr.	No evidence of poisoning until end of period, with jaundice, acute liver damage and death	Autopsy: Liver weighed 538 gm. Acute toxic necrosis.
15	Reichle,[21] 1929	C.	31,150 gr. in 1926	No symptoms	Autopsy: Liver weighed 757 gm.
		C.	21,100 gr. in 1927	No symptoms	Diagnosis: Yellow atrophy.
		C.	1800 gr. 1928	Epigastric pain, tenderness, weakness, jaundice, confusion, twitchings, convulsions, death	
16	Evans and Spence,[4] 1929	C., 5 to 6 gr. doses at irreg. intervals for 3 yrs.	Unknown	No symps. appeared until end of this time when he lost weight, with dizziness, weakness of legs, rapid heart. No skin rash	Recovered. All symptoms disappeared when drug was stopped.
17	Tak,[25] 1930	A.	150 gr.	No symptoms	Recovered 6 wks. later.
		A. at later date	45 gr.	Anorexia, enlargement of liver and jaundice	
18	Rabinowitz,[3] 1930	C., 10 gr. at irreg. intervals for 2 mos.	Probably 200 gr.	No symps. until at end of 2 mos. period; then jaundice and itching	Recovered after illness of 2 mos.
19	Ross,[23] 1931	T., several courses of treatment	Unknown	No symps. until final course of treat. followed by pain, vomiting, fever, jaundice, delirium, ascites, death	Autopsy: Liver weighed 670 gm. with necrosis of hepatic cells and evidences of regen.
20	Walker,[26] 1931	C., over long period	750 gr.	No symptoms	Autopsy: Liver weighed 650 gm. Hepatic cells showed evidence of necrosis and regen.
		C., 7½ gr. t.i.d.	125 gr.	Heartburn, nausea, jaundice vomiting, incr. in size of liver, delirium, death	
21	Parsons and Harding,[16] 1932	Rentons Hydracine tablets for 6 mos.	1000 gr.	No app. symps. until end of this period. Epigastric distress, vomiting, gradually deepening jaundice, death	Autopsy: Liver weighed 750 gm. and was necrotic.
22	Reah,[20] 1923	C., 7 gr. t.i.d. for 2 weeks; 1 mo. later a 2d course over 2 weeks	About 300 gr.	No symptoms	Necropsy revealed red atrophy of the liver.
			300 gr.	Shortly after the 2d course, nausea, anorexia, jaundice, death	
23	Weir and Comfort,[27] 1933	A.	500 gr.	No symptoms until end of period; then toxic cirrhosis	Recovery when these drugs were stopped and a high carbohydrate diet given.
		C., over 2 yrs.	500 gr.		
24	Perkel,[17] 1933	A., in 4 days	100 gr.	No symptoms	Autopsy: Liver weighed 400 gm.
		C., 2 mos. later over 9-day period	200 gr.	Symps. of liver damage, jaundice, death	Diagnosis: toxic necrosis.
25	Bloch and Rosenberg,[2] 1934	F. 7 to 15 gr. daily for 18 mos.	3000 gr.	No symps. until the end of period; then vague symps. of toxicity (no jaundice), death	Autopsy: Liver weighed 1250 gm. and toxic cirrhosis was present.

TABLE 1.—*Continued*

Case No.	Reference.	Drug and dose.	Total dose.	Symptomatology.	Result.
26	Palmer, Woodall and Wang[15]	C. in unknown amounts for indefinite period. Later 24 tablets	Unknown 180 gr.	No symptoms Evidence of liver damage, death. No jaundice	Autopsy: Liver weighed 1051 gm.; acute toxic cirrhosis.
27	Bloch and Rosenberg,[2] 1934	Novatophan 10 gr. daily June, 1932 No treat. for 3 mos.	75 gr. 125 gr. for next 3 mos.	No symptoms Weakness, nausea, vomiting, loss in wt. light colored stools. Death 2 mos. later. No jaundice	Autopsy: Liver weighed 700 gm.; yellowish-green, subacute necrosis.
28	Sugg, 1932 (Case 2)	A., gr. 5, t.i.d. for 14 days Nov., 1931 A., Jan., 1932	200 gr. Unknown	Had taken A. for years at irreg. intervals with no toxic effects, until Nov., 1931; then jaundice, loss of appetite and wt. and clay-colored stools Second attack of jaundice following A.	All symptoms disappeared when drug was stopped. Recovered 6 wks. later after all A. was stopped
29	Sugg, 1933 (Case 3)	A., at intervals for years, Jan., 1933 A. A., 6 tablets within 2 wks.	Unknown Unknown 20 gr.	No symptoms during this period Jaundice, clay-colored stools, nausea Nausea, weakness, jaundice, fluid in abdomen. In hosp. 4 mos.	Recovered. Recovered.
30	Sugg,1934 (Case 4)	A. for several years A., May, 1934	Unknown Unknown	No symptoms during this period Deep jaundice and extreme illness, death	Liver: Ac. yellow atrophy.
31	Sugg, 1935 (Case 5)	A., for 2 or more yrs., irreg. A., 10 gr. daily for 10 days, in March, 1935	125 gr. early part of 1934, 250 gr. 4 mos. later 100 gr.	No symptoms No symptoms Loss of appetite, weakness, jaundice, generalized itching, liver became large and tender	Recovered after ac. illness of 6 wks. duration. No harmful effects occurred until 3rd course.
32	Sugg, 1936 (Case 6)	A., for several years, irreg. A. for 3 wks. in 1934 A., 5 gr. doses for 1 mo., 1935	Unknown 75 gr. Between 75 and 100 gr.	No symptoms No symptoms Jaundice in 2 wks. after drug was begun. Deepened, and was followed by weakness, loss of wt., itching, bile in urine, clay-colored stools. Abd. distended, liver big and tender	Recovered after ac. illness of 3 mos. Liver not normal in size until 1 yr. later.

phenomenon of an acquired sensitivity or susceptibility to this drug. The case histories of other observers as well as my reports are divided into two groups: 1, A cutaneous group of 10 cases with 2 deaths; 2, a hepatic group of 22 cases with 12 deaths.

2. Many theories have been advanced as to the exact cause of the toxicity of cinchophen, only 2 of which are discussed here: (*a*) That the necrosis of the liver which almost invariably results, is due to an abnormal susceptibility of the individual because of certain predisposing conditions; (*b*) that the various toxic manifestations of cinchophen are allergic in nature.

3. An individual may not show toxic symptoms from the use of cinchophen upon its first administration, nevertheless, damage may have occurred which may be accentuated by readministration, even after several months or years.

4. The mechanism of acquired sensitivity from non-protein substances, such as cinchophen, is not understood. Landsteiner and others believe that an antigen antibody mechanism explains hypersensitivity, though it is unproven.

5. Reports of toxic cirrhosis definitely attributed to cinchophen are increasing. The relationship between this drug and liver damage was not understood until recent years, even in the presence of jaundice, and toxic cirrhosis without jaundice was not appreciated at all.

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A COMPARISON OF INTRACUTANEOUS REACTIONS IN MAN TO THE PURIFIED PROTEIN DERIVATIVES OF SEVERAL SPECIES OF ACID-FAST BACTERIA.*

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The specificity of the tuberculin reaction in man is seldom questioned. Krause[11] in 1916 concluded: "it would appear that there

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is no cutaneous hypersensitiveness without a focus (tubercle)." And Hart,[8] in 1932, in a monograph on the tuberculin test says: "and if the words 'under natural conditions' are added, and possible cross-reactions within the species are excepted, this (Krause's) view is held by most workers today."

On the other hand, the specificity of the tuberculin reaction in cattle has been questioned, because the percentage of tuberculin-reacting cattle showing no macroscopic lesions of tuberculosis upon autopsy has steadily increased, and because the percentage of such animals in all the cattle tested has remained practically constant, as the program for the eradication of tuberculosis in cattle has progressed. In 1922 in the United States 8.7% of the cattle reacting to the intracutaneous test showed no macroscopic lesions of tuberculosis. And in 1936 in Wisconsin of 2343 reacting cattle, 33% showed no macroscopic lesions and 12% showed skin lesions only. Crawford[5] concludes that the majority of these no-visible-lesion tuberculin-reacting cattle in the United States have microscopic lesions of tuberculosis, but that some may be infected with human or avian tubercle bacilli. The etiology of the skin lesions is unknown; microscopically acid-fast organisms are found in the lesions, but tubercle bacilli cannot be cultivated therefrom, and many workers believe that acid-fast bacteria from the soil are the causative agents.

In Wisconsin, Hastings and co-workers[9] recovered saprophytic acid-fast bacteria from the lymph nodes of no-visible-lesion tuberculin-reacting cattle, and by injecting massive doses of these organisms succeeded in sensitizing non-tuberculous cattle to tuberculin. Hastings and co-workers[10] isolated avian tubercle bacilli from the lymph nodes of a no-visible-lesion tuberculin-reacting cow, and McCarter, Hastings, and Beach[14] isolated avian tubercle bacilli from the lymph nodes of 3 out of 28 tuberculin-reacting cattle showing minimal lesions of tuberculosis.

Since, then, cross reactions within the genus of acid-fast bacteria are responsible for the non-specificity of some reactions to mammalian tuberculin in cattle, such cross reactions might also be responsible for some reactions to mammalian tuberculin in man. The failure of some 80% of University of Wisconsin students reacting to tuberculin to show either healed or active tuberculous lesions upon chest *x*-ray indicates the possibility of sensitization by some agent other than the human or bovine tubercle bacillus. Undoubtedly a few of these individuals have extra-pulmonary tuberculous lesions; and presumably the majority of them have pulmonary lesions which either are very small or have healed and left no traces, because pathologists will admit that in many autopsies minimal lesions of tuberculosis are missed. Conceivably, some of these minimal tuberculous lesions in man may be caused by some species of acid-fast bacteria commonly considered non-pathogenic for man.

The survey reported here on the comparative testing of university

students with the purified protein derivatives (P.P.D.'s) of the human and of the avian tubercle bacillus and of *Mycobacterium smegmatici* was made to find whether these other mycobacteria were responsible for the sensitization of some individuals to human tuberculin.

Tests with avian tuberculin have been reported. Seibert and Morley[19] using P.P.D.'s, tuberculins standardized as to the weight of active principle present, showed a quantitative specificity in the reactions of tuberculous guinea-pigs to human and avian tuberculins. The results of Fenger and co-workers[7] in testing man with an avian MA100 tuberculin (another chemically standardized tuberculin first prepared by Masucci and McAlpine[15]) also suggested that human and avian tuberculins might be quantitatively, if not qualitatively, specific for sensitization by the homologous organism; but the method used by these workers was not designed to investigate the specificity of the tuberculin reaction. The results of the comparative testing of man with human and avian Old Tuberculins reported by Dolgopol[6] and Branch[4] are invalidated because of a combination of two factors: O.T.'s vary widely in their content of active principle and cross reactions to avian tuberculin occur in humans sensitized by mammalian tubercle bacilli.

In this study we were concerned primarily with sensitization to tuberculin by the avian tubercle bacillus as it might affect reactions to mammalian tuberculin, rather than with the production of manifest disease by the avian type. Sensitization to tuberculin could be caused by the presence of avian tubercle bacilli in the body, even if they did not produce detectable disease. The organisms might enter the body through the intestinal tract by the ingestion of infected eggs or through the respiratory tract by breathing contaminated dust.

We have considered also one other factor which might be responsible for tuberculin reactions in individuals never infected with human or bovine tubercle bacilli; namely, sensitization by tuberculin itself. Seibert[18a] has found the human P.P.D. to be nonsensitizing for guinea pigs. Aronson and Nicholas[2] have reported sensitization of man by the MA100 tuberculin, the second injections being given 3 months after the first. Steele and Willis[21] have found that by giving repeated injections of tuberculin at intervals of 2 days, practically all children can be sensitized to tuberculin. The small amount of work which has been done indicates that the average size of the molecules in the particular tuberculin used may determine its power to sensitize.

Technique. *Purified Protein Derivatives.* The human, bovine, and avian tuberculins used were the purified protein derivatives kindly supplied us by Dr. Seibert of the Phipps Institute. The protein derivative of *Mycobacterium smegmatici* was prepared for us by Seibert's method through the courtesy of Dr. Reichel of the Mulford Biological Laboratories of Sharp and

Dohme. The human Old Tuberculin came from the Saranac Lake Laboratory. The tuberculins were all diluted from the stock solutions by one of the authors, using chemically clean glassware, and pipettes rather than syringes.

Dosage and Injection. The standard doses of P.P.D. prescribed by Long, Aronson, and Seibert[13] were used throughout. Of O.T. the weak dose was 0.01 mg. and the strong dose 1.0 mg. The human P.P.D. and the P.P.D. to be compared therewith were injected simultaneously by different operators one in each forearm. The volume given was standardized by the size of the bleb raised. "Sterile" needles were used for each student, the needles for each P.P.D. being separately "sterilized" in boiling water throughout the day.

Reading of Reactions. The standards of Aronson[1] were used in grading the reactions. An edema of less than 5 mm. in diameter, or erythema of more than about 10 mm. in diameter was noted on the records, but for statistical purposes such reactions were called negative.

Chest Roentgenograms. The chest *x*-rays were single anteroposterior films taken by the *X*-ray Department of the Wisconsin General Hospital, and were read independently by 2 individuals.

Selection for Statistics. In compiling our statistics, we used only the data on those students who were from 18 to 23 years of age, and who reported on schedule so that their reactions could be read about the 48th hour.

Experimental. *A. Avian P.P.D.* Comparative tests with human and avian P.P.D.'s were made on two unselected groups of 500 Freshman men each. Similar comparative tests were made on one

TABLE 1.—REACTIONS OF UNIVERSITY MALE STUDENTS TO HUMAN AND AVIAN P.P.D.'S AND FINDINGS OF CHEST *X*-RAYS OF POSITIVE REACTORS.

Number and group of students.	Reactions to P.P.D.'s.	%	Chest *x*-rays.				
				Group.†			
			No.*	1 (%).	2 (%).	3 (%).	4 (%).
739 Freshman	Human + and Avian +	23.8	172	68.0	23.8	6.4	1.8
	Human + and Avian −	0.4	3	66.7	0	33.3	0
	Human − and Avian +	22.3	161	90.7	8.1	1.2	0
	Human − and Avian −	53.5	0				
125 Agricultural Short Course (Farm)	Human + and Avian +	21.6	27	74.1	25.9	0	0
	Human + and Avian −	0.8	1	100.0	0	0	0
	Human − and Avian +	33.6	0				
	Human − and Avian −	44.0	0				
162 Agricultural Short Course (Farm)	Avian +	53.7	82	92.7	6.1	1.2	0
	Avian −	46.3	0				

* Some students failed to report for *x*-rays and so the number of *x*-rays will not agree in all cases with the number of reactors.

† Key to *x*-ray groups:

1. No pathologic changes; or some evidence of previous disease of questionable etiology, *e. g.*, adhesions, thickened trunks, etc.; or organized deposits which may be calcium but nature questionable.
2. Calcium in Ghon tubercle, hilum nodes, or both (primary tuberculosis).
3. Infiltration with questioned activity (activity can be proved only by extended study of the patient).
4. Active adult tuberculosis (activity proved by detailed laboratory and clinical study of the patient).

unselected group of Agricultural Short Course students,* and tests with avian tuberculin only on another unselected group of Short Course students, since it was thought that the two tuberculins given simultaneously might be acting as a stronger dose of one of the tuberculins and causing more reactions. Chest *x*-rays were taken of all positive reactors (except on the reactors to avian in one group of farmers). The results of the tests and the *x*-ray findings are placed in Table 1, the results on the two Freshman groups being combined because the differences were not significant.

Three phenomena are brought out in Table 1: 1, with the exception of 3 students, all students reacting to human tuberculin also reacted to avian; 2, a relatively large number of students reacted to avian and not to human, the percentage of such reactors being greater in the Short Course group than in the Freshman group; and, 3, some of the students who reacted to avian and not to human showed calcified lesions of tuberculosis upon *x*-ray. Thus, the results were unexpected and their significance is not self-evident. Therefore, our interpretation of them will be reserved for the discussion on all the data.

The results on testing the Short Course students with avian P.P.D. only showed that probably one dose of tuberculin injected alone elicits the same reaction as when 2 doses of tuberculin are given simultaneously on opposite arms, since the total percentage of Short Course students reacting to avian P.P.D. in the one group was not significantly different from the total percentage reacting in the second group.

The tabular data give only a comparison of the qualitative reactions to avian and human tuberculins, but quantitative relationships were also observed. The strong reactors we shall arbitrarily call those who react to the first dose or who react 3+ or 4+ to the larger dose, and the weak reactors those who react 1 or 2+ to the larger dose. We found that *all* strong reactors to human P.P.D. reacted less to avian P.P.D., while the weak reactors to human reacted in the same degree to avian, that is, all individuals reacting strongly to avian P.P.D. were more sensitive to human P.P.D. The significance of these data also will be discussed later.

Two control groups of *x*-rays were obtained on a part of the students who reacted to neither human nor avian P.P.D. The combined results on the two groups in Table 2 show that none of these students had healed or active tuberculous lesions; the *x*-ray of one individual showed an infiltration similar to the infiltrations of early tuberculosis, but the diagnosis could not be confirmed because the student failed to report for further examination. So that according to Tables 1 and 2, all individuals with calcified lesions reacted to avian tuberculin.

* All Agricultural Short Course students come from farms.

TABLE 2.—FINDINGS ON THE CHEST *X*-RAYS OF MALE STUDENTS WITH NEGATIVE REACTIONS TO BOTH HUMAN AND AVIAN P.P.D.

Group of students.	No.	Chest *x*-ray group. 1 (%).	2 (%).	3 (%).	4 (%).
Freshman	153	98.7	0.6*	0.6†	0

* This student showed on the test with avian tuberculin erythema and edema 3 mm. in diameter.

† This student failed to report for further examination and, therefore, the progress of this lesion has never been checked.

In addition to testing university students with avian tuberculin, we did attempt to test families on farms where the flocks of chickens were badly infected with avian tubercle bacilli. We visited the farms personally, but so much time was required in influencing the farmers to take the test, that it was impossible, without undue expenditure of time and money, to carry out a significant number of tests.

B. Bovine P.P.D. and Smegmatici P.P.D. The P.P.D. from the bovine tubercle bacillus and the P.P.D. from *M. smegmatici* were compared with human P.P.D. in the same way as the avian was. An unselected group of Freshman men in September, 1936, were tested with human and bovine P.P.D.'s, and another unselected group with human and smegmatici P.P.D.'s. Chest *x*-rays were taken on all positive reactors except that funds were not available for films of those individuals reacting to smegmatici and not to human (Table 3). In their qualitative relationships the human

TABLE 3.—REACTIONS OF UNIVERSITY MALE STUDENTS TO HUMAN AND BOVINE AND TO HUMAN AND SMEGMATICI P.P.D.'S AND FINDINGS ON THE CHEST *X*-RAYS OF THE POSITIVE REACTORS.

Number and group of students.	Reactions to P.P.D.'s.	(%).	Chest *x*-rays. No.	Group. 1 (%).	2 (%).	3 (%).	4 (%).
394	H + and B +	25.1	97	64.9	33.0	2.1	0
Freshman	H + and B −	4.6	16	87.5	12.5	0	0
	H − and B +	0.5	2	0	100.0	0	0
	H − and B −	69.8	0				
464	H + and S +	14.0	60	88.3	11.7	0	0
Freshman	H + and S −	6.0	28	67.9	21.4	7.1	3.6
	H − and S +	9.9	2	50.0	50.0	0	0
	H − and S −	70.1	0				

H = human. B = bovine. S = smegmatici.

and bovine P.P.D.'s are seen to be almost comparable, although about 5% of the students reacted to human and not to bovine, and 0.5% to bovine and not to human. The qualitative relationships of the reactions to human and smegmatici P.P.D.'s differed both from those to bovine and those to avian; some students reacted to smegmatici and not to human P.P.D., but the percentage

was only about half that of those reacting to avian and not to human; and a small but significant percentage reacted to human and not to smegmatici, whereas the number of students reacting to human and not to avian was insignificant.

In comparing the size of reactions to human and bovine P.P.D.'s we found that the reactions were consistently very nearly of the same intensity, some of the reactions to bovine being 4 or 5 mm. larger in diameter than those to human, and other reactions being slightly greater to the human. Furthermore, those individuals who reacted to human and not to bovine were all weak reactors, giving only 1+ reactions to the strong dose. Thus, according to these data, human and bovine P.P.D.'s are of about equal potency, the human being slightly more potent than the bovine for man, and therefore these tuberculins could not be used to distinguish between infections with human and bovine tubercle bacilli. This has been assumed to be true in the testing of cattle since human tuberculin is used almost exclusively for this purpose.

The quantitative relationships of the reactions to smegmatici with those to human P.P.D. were somewhat like those to avian P.P.D. All those individuals who were strong reactors to human reacted less to smegmatici and every individual who gave a strong reaction to smegmatici gave a stronger reaction to human. And again all students who reacted to smegmatici but not to human gave only 1 or 2+ reactions to the large dose. On the other hand, of those who reacted to human and not to smegmatici half reacted to the weak dose and half reacted to the strong dose.

C. Salt Solution Controls. Since the difficulty of removing tuberculin from syringes has been emphasized by Nelson, Seibert, and Long,[17] an unselected group of male students were used as a control group and given injections of 0.85% sodium chloride solution as well as of human P.P.D. Eighteen of the 460 tested reacted to "salt solution." That these reactions were due to contamination of the syringes with tuberculin was proved by reinjecting some of these same students 6 months later using new (unused) syringes and needles. The reactions to NaCl occurred in very strong reactors to tuberculin, all these students being sensitive to the small dose, and the reactions were much smaller to the NaCl than to the tuberculin. These facts, together with the fact that the number of reactors was small, cause us to conclude that contamination with human tuberculin could not have been responsible for the consistent occurrence of cross-reactions to avian and bovine P.P.D.'s in individuals sensitive to human P.P.D. It is possible but not probable that all the cross-reactions to smegmatici P.P.D. were due to contamination of the syringes with human P.P.D., since some students who reacted to human did not react to smegmatici. And, of course, none of the other data could be questioned on this basis, since reactions to the other P.P.D.'s in individuals not sensitive to human

P.P.D. could not have been caused by contamination with human P.P.D.

D. Sensitization by Tuberculin to Tuberculin. The human and avian P.P.D.'s as well as a sample of O.T. were tested for their sensitizing abilities by re-injecting students 6 months after the original test. This period of time was chosen since it is the interval between retests recommended by the Student Health Committee of the National Tuberculosis Association.[23]

So that O.T. could be compared with P.P.D. in its sensitizing potency, an unselected group of 500 Freshman women had been tested with O.T. and 23% found to react.

One group of Freshmen who had been negative to avian P.P.D. were called for a retest with avian P.P.D. 6 months later. Freshmen in the second group who had been tested with avian, and all those who had been tested with bovine or smegmatici P.P.D.'s, and who had not reacted to *human* P.P.D., were retested 6 months later with human P.P.D. The Freshmen women who had not reacted to Human O.T. 6 months before were retested with O.T. diluted from the same batch of concentrated tuberculin. These results are all included in Table 4.

TABLE 4.—REACTIONS UPON RETESTS WITH HUMAN AND AVIAN P.P.D.'S AND HUMAN O.T. 6 MONTHS AFTER THE ORIGINAL TEST.

Tuberculin used for retest.	Reactions to original test.	Number retested.	Reactions upon retest.	
			Pos. (%).	Neg. (%).
Avian P.P.D. . . .	Human − and Avian −	137	33.5	66.4
Human P.P.D. . . .	Human − and Avian +	44	31.8	68.2
	Human − and Avian −	86	4.6*	95.4
	Total Human −	130	13.8	86.2
Human P.P.D. . . .	Human − and Bovine +	1	100.0	0
	Human − and Bovine −	132	6.1	93.9
	Total Human −	133	6.8	93.2
Human P.P.D. . . .	Human − and Smegmatici +	21	4.8	95.2
	Human − and Smegmatici −	174	4.0	96.0
	Total Human −	195	4.1	95.9
Human O.T.	Human O.T. −	201	10.4	89.6

* These individuals all showed on the original test to avian P.P.D. an erythema of more than 10 mm. in diameter but only slight edema (less than 5 mm. in diameter).

All the reactors positive to the test with human tuberculin were *x*-rayed, but the *x*-ray findings are not tabulated because the films showed no evidences of either healed or active tuberculosis. *X*-rays were not obtained on those reacting to the retest with avian P.P.D.

The number of students reacting to the retest with avian P.P.D. was surprisingly large; 46 out of 137 (about $\frac{1}{3}$), had become positive

reactors within 6 months. These reactions were almost certainly caused by sensitization by the tuberculin itself, because it seems unreasonable that sensitization was caused by infection with any type of tubercle bacillus.

On the other hand, the human P.P.D. does not sensitize according to the following evidence. In the avian group all who reacted to the retest with human P.P.D. had shown some sensitivity to *avian* P.P.D. 6 months before, although a few of these individuals had had reactions with too small an area of edema to be called positive. This observation, together with the fact that no lesions of tuberculosis were found on the *x*-rays of the reactors to the retests, means that the original injection of avian tuberculin increased an already existing sensitivity in these individuals so that they reacted upon a second injection of human P.P.D. This also means that those individuals in the bovine and smegmatici groups who reacted upon the retest to human P.P.D. would have reacted 6 months before to avian P.P.D. The percentage of reactors upon retest with human P.P.D. in the bovine and smegmatici groups is about the same, an average of about 5% for the two groups, while the percentage of reactors in the avian group is over twice as great. Statistical analysis showed the difference to be significant, and proves that the "population" in the avian group is different from the "population" in the combined bovine and smegmatici groups. The only experimental variable in the two groups is that one was injected with avian tuberculin, and therefore the conclusion is that the avian tuberculin is more potent than human or bovine or smegmatici P.P.D. in increasing the slight sensitivity of individuals who do not give reactions upon the first injection of human tuberculin.

The percentage of reactors to the retest with O.T. is slightly greater than the percentage of reactors to the retest with human P.P.D. in the bovine and smegmatici groups. However, with the comparatively small numbers of persons examined, the difference is not sufficiently great to be statistically significant, so that we cannot conclude that the O.T. is more potent in increasing sensitivity than the human P.P.D.

As a further test of sensitization by O.T., the reactions to human tuberculin were compared in the Freshmen who had had tuberculin tests in high school in the last year and in those who had never had such tests. No correlation was found, the percentage of reactors to the university test being about the same in both groups. Of course, very few of the students had had more than one test in high school, and probably only a weak dose of 0.01 or 0.1 mg. of O.T. had been used. With the tests now given annually, some effect may be found in the future.

E. Significance of Erythematous Reactions. According to the present standards, reactions with less than 5 mm. of edema are

called negative even though considerable erythema may be present. We have taken chest *x*-rays of 17 women, all of whom had reactions which would be called negative but had erythema of more than 10 mm. in diameter. The *x*-rays of 3 of these individuals showed calcified lesions of tuberculosis. Also as noted above, such substandard reactions to avian P.P.D. indicated some sensitization to tuberculin as shown by reactions upon retest. A phase of erythema with no edema was observed by Mote and Jones[16] as the initial stage in experimental skin sensitization to serum protein, the edema appearing later; the sensitization disappeared in opposite order, erythematous reactions being the last evidence. Erythematous reactions, which are too large to have been induced by the needle prick, are, then, probably evidence of sensitization to tuberculin.

Discussion. *A. Specificity of Purified Protein Derivatives from Different Species of Acid-fast Bacteria.* We attempted to find whether human beings might be sensitized to human tuberculin by acid-fast bacteria other than the human or bovine tubercle bacillus, by making comparative tests on university students with the purified protein derivative tuberculins of the avian tubercle bacillus and of the smegma bacillus. We found that we could not solve our problem by this method, because the reactions to these protein derivatives could not be explained on the basis of our present knowledge of tuberculin and of the tuberculin reaction.

The reactions to avian and smegmatici tuberculins in persons with strong reactions to human tuberculin can be explained as cross reactions, because they were all less in degree than the reactions to human. These quantitative relations in the reactions to avian and smegmatici tuberculins show that these protein derivatives are not so closely similar to the human protein derivative as that of the bovine tubercle bacillus, since the severity of the reactions to bovine P.P.D. was of the same degree as that of the reactions to human in the same individuals.

On the other hand, the reactions to avian and smegmatici in weak reactors, or in non-reactors, to human P.P.D. cannot be explained with our present knowledge. The following evidence is against the explanation that these reactions are specific, *i. e.*, that they are due to sensitization by the avian tubercle bacillus or by the smegma bacillus:

1. The consistency in the quantitative relations of reactions to human and to avian or smegmatici P.P.D.'s disappears in the group of individuals reacting only 1 or 2+ to the strong dose of human P.P.D.: these all react in about the same degree to the avian or to the smegmatici as to the human.

2. The number of individuals reacting to avian P.P.D. and not to human is relatively large, and these reactions are all weak, being only 1 or 2+ to the strong dose.

3. The reactions to avian P.P.D. in individuals not sensitive to human P.P.D. cannot be correlated with rural residence of these individuals. About 70% of such individuals live in cities with populations of over 2500.

4. The evidence all points to a difference in the antigenicity of the human P.P.D. and of the avian P.P.D. Our experimental evidence for this is that one injection of avian P.P.D. sensitized one-third of the individuals tested to a second injection of the same substance, whereas human P.P.D. does not sensitize. This difference in antigenicity may be that the avian P. P. D. consists of molecules of larger average size than those of the human P.P.D., since Seibert[18b] has shown that the size of the molecule determines whether or not various tuberculins will sensitize experimental animals. And Aronson and Nicholas[2] have demonstrated the sensitization of human beings by the human MA100 tuberculin which has a higher molecular weight than the human P.P.D. tuberculin. Confirmatory evidence to this hypothesis is also given by the work of Barnwell and Pollard[3] on University of Michigan students. They found by using the human T.P.T. (the protein precipitated by trichloracetic acid) tuberculin, which also has a higher molecular weight than the human P.P.D. tuberculin, about the same percentage of reactors as we did by using the avian P.P.D. Also they found almost twice as many reactors with the human T.P.T. as with human O.T., whereas we found about twice as many reactors to avian P.P.D. as to human P.P.D. Barnwell and Pollard state that T.P.T. tuberculin does not sensitize but we should like to question this interpretation of their results. They found by giving 7 or more tests to students and nurses over a period of from 1 to 20 months that 27 of the total of 46 became positive. Is not such a percentage of reactors upon retest rather high to assign to infection with tubercle bacilli within a period of 20 months?

According to our hypothesis the human and avian P.P.D.'s are quantitatively specific in highly sensitive individuals, but less sensitive individuals react in the same degree to avian as to human because of the greater antigenicity of the avian. The slightly sensitive individuals who react to avian P.P.D. but not to human P.P.D. may have been sensitized by the human tubercle bacillus, but the human P.P.D. cannot elicit a reaction whereas the avian P.P.D. can by virtue of its greater antigenicity. Such reactors may also have been sensitized by the avian tubercle bacillus, and our data on the students from farms, the Agricultural Short Course boys, show that this probably occurs. A combination of the data gives a total of about 54% of 287 agricultural students reacting to avian and of about 46% of 739 Freshmen, and upon statistical analysis it proves to be very probable that this difference is significant.

In making the P.P.D. tuberculins the protein molecules are hydrolyzed in the process of concentration by heat and probably also

in the process of precipitation by trichloracetic acid. Therefore no exact control is exercised over the degree of degradation of the protein, and differences in the nature of the proteins of the various species of acid-fast bacteria might well account for the differences in the size of the particles in the tuberculins.

B. The Specificity of the Tuberculin Reaction. The qualitative specificity of the tuberculin reaction must be questioned; we cannot prove with our present knowledge that all reactions to human P.P.D. are due to sensitization by the human or bovine tubercle bacillus, and we know that some individuals with healed lesions of tuberculosis do not react to human P.P.D. We cannot prove that individuals with weak reactions to human P.P.D., *i. e.*, 1+ or 2+ to the strong dose of 0.005 mg., have been sensitized by the human or bovine tubercle bacillus, because such individuals react in about the same degree to the P.P.D.'s of other acid-fast bacteria such as the avian tubercle bacillus and the smegma bacillus. On the other hand, those individuals whose chest *x*-rays show healed lesions of tuberculosis, but who react only to avian and not to human P.P.D., have most probably been sensitized by mammalian tubercle bacilli. But again, that all the reactions to avian P.P.D. in individuals not reacting to human P.P.D. are due to sensitization by mammalian tubercle bacilli has not been proved. Sensitization by other acid-fast bacteria may be responsible for some of the reactions to human P.P.D. and to avian P.P.D. It seems likely that such sensitization may be responsible because acid-fast organisms are omnipresent, occurring both on the membranes of man and in the soil; and because the similarity of the protein derivatives of such acid-fast bacteria as the avian tubercle bacillus, the smegma bacillus, and the phlei bacillus, to the protein derivatives of the human and bovine tubercle bacillus is shown by cross-reactions in man and other animals.

Of course, non-bacterial proteins or proteins of bacteria in other genera may be so related to the proteins of acid-fast bacteria as to produce sensitization to tuberculin. Selter and Tancre[20] found that tuberculous individuals reacted to peptone and casein and to an extract of the cells of *Escherichia coli*. Their solutions of these products may have been contaminated with tuberculin since Nelson, Seibert, and Long[17] found that tuberculin could be removed from syringes and other glassware only by treatment with alkali or dichromate solution. Therefore Selter and Tancre's work is open to criticism and would have to be repeated under rigid control before acceptance.

The tuberculin reaction is quantitatively specific, because all those with active cases of tuberculosis react to human P.P.D. and because all strong reactors to human P.P.D. react less to avian or to smegmatici P.P.D. Barnwell and Pollard[3] found that all individuals with active tuberculosis with one exception reacted to human O.T. and we found with one exception that all students with

active tuberculosis reacted to human P.P.D. The exceptional case of the former authors was one of skin tuberculosis and our case[22] was one of atypical tuberculosis of the lymph nodes; Barnwell and Pollard's patient reacted to human T.P.T. and ours reacted to avian P.P.D. Students whose chest roentgenograms show lesions of questionable activity do sometimes fail to react to human P.P.D., as can be seen from our tabular data, but all such students whose lesions were later proved to be pathologically active* had reacted to human P.P.D. on the original test.

The conception of the tuberculin reaction as being beyond question qualitatively specific was formed because O.T. was used by all workers. According to the graph of Hart[8] where the percentage of reactions in a "normal" population is plotted against the strength of dose of O.T. given, increases in the doses of O.T. above 10 mg. detect very few reactors. But Barnwell and Pollard's[3] graph shows that plotting the percentage of reactors to human T.P.T. against the dose given results in a straight line curve, the percentage of reactors increasing almost proportionally with the dose of T.P.T. given; and the percentage of reactors to the strongest dose of T.P.T., 0.01 mg., being almost twice as great as the percentage of reactors to a dose of 1.0 mg. of O.T. Of course, one cannot reason by extrapolation that if still larger doses of T.P.T. were given, 100% of the population would react, and no experimental data are available on this point. Apparently the difference which accounts for the larger number of reactors to the T.P.T. tuberculin is that this product has a higher molecular weight than the O.T.

The validity of our explanation for the lack of qualitative specificity of the tuberculin reaction cannot be proved until the nature of the difference between the human and the avian P.P.D. is found by chemical methods, and until further evidence is adduced on the effect of the size of the molecule of the antigen upon skin hypersensitivity. There are no observations on the effect of the size of the molecule upon skin reactions in humans or laboratory animals with varying degrees of sensitivity. In fact, very little is known concerning the antigenic nature of protein hydrolysis products even for the precipitin reaction (see Landsteiner,[12] p. 132).

C. The Use of the Tuberculin Test. Our results change our program for controlling tuberculosis in the student body very little, but they give us a sure basis for that program. The tuberculin test with human P.P.D. or with human O.T. remains valuable as an aid to the diagnosis of active cases of tuberculosis. At this University where but 30% of the entering students react to human P.P.D., the active cases can be discovered by the use of the tuberculin test and by chest *x*-rays of the positive reactors, at less than half the cost of *x*-rays only on all the students. In cases where a patient who has a lesion suspected to be of tuberculous origin fails

* The "pathologically active" cases include those which are not clinically active; the activity in such cases was proved by laboratory study.

to react to human P.P.D. or to human O.T., tests with human T.P.T. or with avian P.P.D. should be made before the diagnosis of tuberculosis is questioned. The adoption of human T.P.T. or of avian P.P.D. for routine testing would not be desirable because the possibilities of sensitization by the tuberculins themselves are so great. Testing with avian P.P.D. does find all those who have healed lesions of tuberculosis as well as those with active lesions, but progressive lesions very seldom develop in these individuals with calcified lesions in the experience of one of the authors (R. H. S.). Again some individuals with healed lesions give sub-standard reactions to human P.P.D. and the physician will have to use his own judgment as to whether the cost of *x*-rays on all individuals with sub-standard reactions is justified by the finding of some calcified lesions. Intervals of 6 months between retests with human P.P.D. are sufficient to preclude possible sensitization by human P.P.D. according to our results; according to the results of Steele and Willis[21] short intervals between retests may not preclude sensitization. The value of tuberculin tests of negative reactors at intervals of 6 months should be questioned; of 458 students retested with human P.P.D. after 6 months, 35 reacted and none of them showed either healed or active lesions upon *x*-ray. Probably, retests at intervals of 1 year are sufficient. The great majority of those students who give positive reactions 6 months after giving negative reactions have not been infected with tubercle bacilli, but merely their sensitization to tuberculin has been increased by the initial injection of tuberculin, because *all* the students in the avian group who reacted upon retest with human P.P.D. in February, 1937, had been sensitive to avian P.P.D. in September, 1936.

On the other hand, the percentage of reactions to human P.P.D. or to human O.T. can no longer be used as an accurate measure of the extent of infection of the population with tubercle bacilli. Thus, we have no method of estimating the number of individuals who have or have had infection with tubercle bacilli, because we do not know the significance of reactions to human T.P.T. or to avian P.P.D. tuberculin in individuals who do not react to human P.P.D. or O.T.

Conclusions. 1. Intracutaneous reactions to the purified protein derivatives (P.P.D.'s) of the various acid-fast bacteria are not qualitatively specific.

2. The bovine P.P.D. is very similar in nature to the human P.P.D.

3. The avian and smegmatici P.P.D.'s differ from the human P.P.D. in nature and also in antigenicity.

4. Under the conditions of our experiment, avian P.P.D. has sensitized man while human P.P.D. has not, although one injection of human P.P.D. will increase an already existing slight sensitivity.

5. Almost 100% of the students with active tuberculosis react to human P.P.D. All students with calcified tuberculous lesions

react to avian P.P.D., but some of them fail to react to human P.P.D.

6. The tuberculin test is useful in a public health program for the detection of active cases of tuberculosis in a large group such as the university student body, because it can be used to select those who should have chest *x*-rays. But it should be used as an indication rather than as an exact measure of the extent of infection with tubercle bacilli in the general population, because not all individuals with healed or active tuberculous lesions react to human P.P.D. or O.T., and because we cannot prove that all individuals who react to human P.P.D. or O.T. have been sensitized by the human or bovine tubercle bacillus. Some reactors may have been sensitized by other mycobacteria commonly considered non-pathogenic for man.

7. More knowledge of the chemistry of the various tuberculins will materially aid in the interpretation of reactions to these tuberculins.

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THE COMPOSITION OF HUMAN BONE IN CHRONIC FLUORIDE POISONING.

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The toxic effects of fluorides on experimental animals are well known.[6,13] In contrast, there are few extensive data on man,

although many instances of acute poisoning by soluble fluorides are recorded.[14,16a,20] Until recently only 1 case of chronic poisoning, attributed to fluorides in beer, has been reported.[19a] There is, however, a well-known relationship between the amount of fluorides in drinking water and the incidence of mottled enamel or chronic endemic dental fluorosis.[5] In this condition both bones and teeth showed a marked increase in fluorine content.[4] Factory workers exposed to cryolite dust showed extensive skeletal changes characterized by massive sclerosis of the bone and increased opacity to Roentgen rays.[15] In 2 of these workers who came to necropsy the bones were chalky white and abnormally large, showed extensive sclerosis, and gave an ash which contained a maximum of 1.31% fluorine.[16b,c]

The present report deals with the composition of bone from a case of chronic fluoride poisoning in man. Except for the fluorine content, the analytical data show essentially normal ratios for all constituents studied. Complete Roentgen ray studies, clinical observations and necropsy findings on this patient have been reported.[2,3]

Materials. The patient, a negro, male, aged 48, under treatment for luetic heart disease, had been exposed almost daily for 18 years to finely ground rock phosphate dust containing 3.88% fluorine. A Roentgen ray examination revealed, in addition to cardiac enlargement, very intense shadows of the bones in the trunk, osteophytes on the vertebral column, a thickened pelvic girdle and some calcification in the attachments of the ligaments.[3]

The bones (described in detail with illustrations elsewhere[2]) were thicker and heavier than normal. The external surfaces were covered with chalky white areas, nodular or platelike exostoses and osteophytes. A portion of isolated rib appeared much more opaque to Roentgen rays than did a normal rib of the same external dimensions (Fig. 1). In cross-section the fluoride rib showed an abnormally thick cortex and very prominent trabeculæ. The teeth were very brittle, but were free from any markings characteristic of mottled enamel.

The bones removed at necropsy were defatted and dried by successive extraction with purified ethyl alcohol and anhydrous ether and finally ground to a powder which passed a standard 80-mesh sieve.

Analytical Methods. Bone samples were ignited in the electric muffle furnace for 5 hours at 650° C. and the weight of the ash obtained. Each sample of ash was dissolved in a small amount of normal HCl acid and after adjustment to pH 3.5, the calcium was precipitated and weighed as the oxalate.[25] For the colorimetric phosphate determination[7] bone ash was dissolved in normal HCl and digested at 100° C. for 10 minutes. Fluorine in the bone ash was distilled from perchloric acid[26] and determined by titration with thorium nitrate in the presence of alizarin.[1] Carbon dioxide determinations on dry fat-free bone were made by the manometric procedure, using the details given by Shear and Kramer.[22]

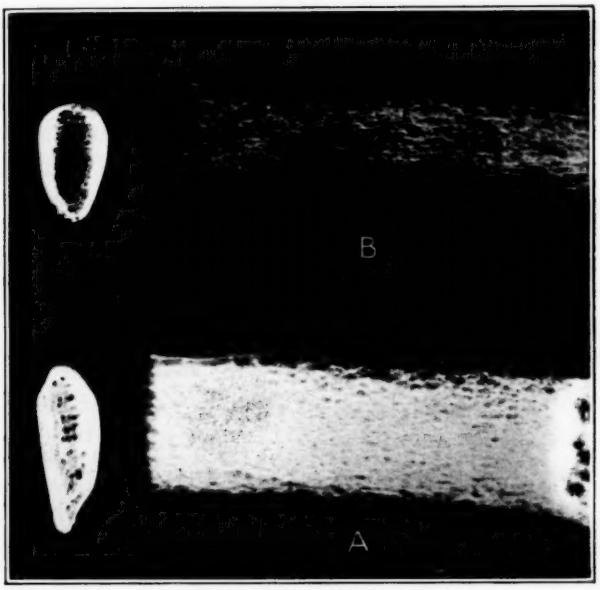

FIG. 1.—Roentgenogram showing; (*A*) increased opacity to Roentgen rays and increased wall thickness of the rib in chronic fluoride poisoning as compared to the (*B*) normal rib.

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Control analyses on normal bone gave satisfactory values. Standard fluorspar gave 46.21% fluorine (theory 46.15%). Phosphate rock used by the plant in which the patient worked averaged 3.88% fluorine in a series of 7 determinations.

Specific gravity determinations were made in the usual manner by weighing bone sections in air and in water, but it was necessary to soak the bones for 24 to 48 hours before making the second weighing. Results are referred to distilled water at 25° C.

TABLE 1.—THE COMPOSITION OF HUMAN BONE IN A CASE OF CHRONIC FLUORIDE POISONING. (RESULTS AS PER CENT OF DRY FAT-FREE BONE.)

Bone.	Ash (%).	Calcium (%).	Phosphorus (%).	Fluorine (%).	Carbon dioxide. (%).
Femur, mid shaft, cortex*	66.47	29.37	11.60	0.29	4.19
Tibia, mid shaft, cortex	65.01	29.32	11.44	0.18	4.16
Ulna, mid shaft, cortex	65.51	29.27	11.67	0.22	4.28
Skull, frontal section	64.19	29.01	11.37	0.38	4.22
Rib, sixth, cross section	66.84	29.24	11.51	0.56	4.25
Sternum, manubrium	64.52	27.51	11.21	0.69	3.93
Vertebra, body of lumbar	65.38	29.01	11.37	0.70	4.14
Vertebral cortex	63.44	.....	.....	0.68	
Osteophyte, vertebral	.....	.....	.....	0.66	
Teeth	74.95	.....	.....	0.10	

* Analytical data expressed as weight per unit volume of bone would be 3.6% below normal values because of the low specific gravity.

Results. Analytical data presented in Table 1 show essentially normal values for ash, calcium, phosphorus, and carbon dioxide. The fluorine content of these bones ranges up to 20 times the values usually considered normal.[6,10,12,13] The results indicate that fluorides accumulated to a greater extent in the softer bones, sternum, ribs and vertebral column, than in the long bones. However, the latter show a fluorine content many times the normal value.

Specific gravity determinations were made on cortical sections of the femurs as removed at necropsy. Results (25°/25°) were as follows: Normal femur A, specific gravity 1.902; normal femur B, 1.903; fluoride femur, 1.833. Similar differences were found in specific gravities of the dry fat-free femurs. Specific gravities of the ribs could not be determined with any degree of accuracy, probably because of air occluded in the spongy structure.

Discussion.—An outstanding characteristic of chronic fluoride poisoning either in man or animal is the accumulation of fluorine in the bones. Values for the fluorine content of bones in our case are comparable to the figures reported for similar studies by others.[4,11,16b,c,21] The same concentrations of fluorine in the body of the vertebra, its cortex and an adjacent osteophyte suggest a state of dynamic equilibrium in this bone. The ratio of fluorine to other constituents is the same whether old bone structure (vertebra) is being recalcified or new bone (osteophyte) formed. Probably the smaller amount of fluorine in the long bones indicates a less mobile equilibrium in these areas as compared with the vertebra.

The fact that we found normal values for carbon dioxide suggests

that the fluorine was deposited as a calcium or magnesium fluoride. Had fluorine entered the crystal to form fluorapatite an equivalent quantity of carbon dioxide should have been displaced. (See studies on carbonate apatite structure of bone.[9,17,24])

Normal figures for calcium and phosphorus suggest that no great disturbance occurred in the mechanism of calcification. Fluorides in small doses over long periods of time apparently stimulate a widespread growth of bone. Although this affected bone is unusually opaque to Roentgen rays, actually it has an abnormally low specific gravity and is, therefore, less dense than normal bone. The increased opacity to Roentgen rays may be attributed to the presence of more bone substance rather than to any increase in the actual density of the bone (Fig. 1).

In certain respects chronic fluoride poisoning in man duplicates that observed in experimental animals. The enlarged chalky white bones with numerous exostoses found in our case and the 2 cases reported by Roholm,[16b,c] are similar to the bony changes which occur in pigs receiving fluorides.[11] These gross physical abnormalities occur in bones with little change in composition. Similar observations have been made on rats.[18] The increased opacity of the bones to Roentgen rays, so prominent in man, has been noted, to a slight degree, in rats,[16d,23] but not in dogs.[8,*] A decrease in the specific gravity of bone in man is duplicated by a similar decrease in the rabbit.[19b] Other similarities have been discussed extensively by Roholm.[16d]

Summary. Human bones from a case of chronic fluoride poisoning contained normal percentages of calcium, phosphorus and carbon dioxide. The fluorine content was increased up to 20 fold the normal value and unequally distributed in various parts of the skeleton, highest in the vertebra and lowest in the long bones. The specific gravity of the femur was low. Data on man and animals are compared.

The authors are indebted to Dr. John T. Bauer for invaluable advice throughout the course of this work, and to Dr. Paul A. Bishop for collaboration, especially for making Fig. 1.

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* According to other investigators,[16d,27] dogs show bone changes detectable by Roentgen ray examination but not identical with those in man.

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PURULENT TYPHOID MENINGITIS WITH RECOVERY.

CASE REPORT.

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MENINGEAL infection due to Bacillus typhosus is a rare complication of typhoid fever; its occurrence in the absence of clinical typhoid fever is exceedingly unusual; recovery from it apparently unheard of.

The subject has been reviewed most recently by Bayne-Jones[2] and Baumgartner and Osen.[1] Prior to 1920, 27 unequivocal cases of purulent typhoid meningitis had been reported. Since then 23 cases have appeared in the literature. All cases of purulent typhoid meningitis thus far reported have been fatal. Meningitis associated with typhoid infections has been divided into 3 types: 1, meningismus or the occurrence of meningeal signs in the absence of any meningeal lesions, *i. e.*, a non-specific toxic reaction; 2, serous meningitis, in which there are symptoms of meningitis with lymphocytosis in the spinal fluid and actual bacterial invasion, edema of brain, round-cell infiltration and a serous exudate; 3, purulent meningitis, *i. e.*, showing predominance of neutrophils in the spinal fluid as well as positive cultures for B. typhosus. This form of meningitis is quite often preceded by the serous form. It has been noted by Baumgartner and Osen[1] and Fernet[3] that cases of typhoid meningitis usually have a minimal enteritis or other common lesions of typhoid fever.

Case Report. CASE L. L. (A–65213).—A 42-year-old white male was admitted to this hospital on March 28, 1936 (twenty-sixth day of disease) because of chills, fever, headache, drowsiness and photophobia. On March 2, 1936 (first day of disease), after an alcoholic debauch, patient suffered a sudden, severe, shaking chill, felt feverish and developed severe headache and marked anorexia. On the fourth day of the disease projectile vomiting was noted in addition to the above symptoms. The neck was stiff

but lumbar puncture was refused. Vomiting subsided on the sixth day of the disease but chills and fever persisted. Because of persistent meningeal signs, patient was sent to a hospital on the ninth day of disease. Lumbar puncture afforded considerable temporary relief from the headache but chills and fever persisted. On the nineteenth day the patient left the hospital against advice. Between the twentieth and twenty-fourth days patient was at home having persistent headache, chills and fever. Drowsiness and photophobia also developed during this time. Spinal fluid was grossly cloudy on the twenty-sixth day of disease when the patient was sent to this hospital.

Past history was irrelevant. Patient had never had typhoid fever and had never been vaccinated for typhoid.

Examination revealed a middle-aged Polish male, both acutely and seriously ill. Pupils were equal and reacted normally. External ocular movements were normal. Optic disks were normal. Stiff neck, bilateral Kernig and positive Brudzinski signs were noted. Moderate dullness with suppression of breath and voice sounds was noted at the right base. No râles were heard. Heart was essentially normal. Spleen was not palpable. No rose spots were seen. Reflexes were physiological.

Laboratory Data (Table 1). Kahn test was negative. Urine was normal.

TABLE 1.—LABORATORY DATA.

Day of disease.	Spinal fluid.						Cultures.				Serologic data.			
	Pressure.	Pandy.	Appearance.	Cell count, % polys.	Smear.	Culture.	Blood.	Bile.	Stool.	Urine.	Widal, blood.	Widal, C.S.F.	Pt's. ser. vs. pt's. org.	Pt's. C.S.F. vs. pt's. org.
9	..	4+	Clear	800 (30)	Neg.									
14	..	4+	....	1200 (2)	Neg.	.....	...	...	...	...	Neg.			
17	..	4+	Cloudy	1200 (2)	Neg.	Neg.								
26*	250	4+	Purulent	3420 (70)	Neg.	Gram neg. rods. Diphtheroids	Neg.							
27	160	4+	Turbid w. shreds	750 (50)	Neg.	Neg.								
29	145	4+	Cloudy	386 (22)	Neg.	Gram neg. rods								
31	170	4+	Ground glass w. shreds	1100 (60)	Neg.	Gram neg. rods	Neg.							
36	..	..	....	....	....	.....	Neg.	...	...	...	Neg.			
37	60	4+	Ground glass	1630 (64)	Neg.	Gram neg. rods	...	...	...	...	...	...	Neg.	
38	..	..	....	....	....	.....	...	...	B. coli	...				
39	..	..	....	....	....	.....	...	...	...	Neg.				
42	760	4+	Ground glass w. shreds	840 (70)	Neg.	No growth	Neg.							
43	..	..	....	....	....	.....	...	...	...	Neg.				
44	140	4+	Ground glass	480 (78)	...	No growth								
46	..	..	....	....	....	.....	...	...	B. coli					
47	140	4+	Clear	146 (40)	...	No growth	...	...	B. coli				Neg.	
50	225	4+	Ground glass w. few shreds	804 (32)	...	No growth	...	...	...	...	...	...	...	Neg.
53	105	4+	Clear	142 (30)	...	Staph.†	...	...	B. coli					
58	135	4+	Clear	80 (3)	...	No growth								
59	..	..	....	....	....	.....	...	Staph.						
63	210	..	Clear	0	...	No growth	...	...	...	...	Neg.	...	...	Neg.
64	..	..	....	....	....	.....	...	Neg.	...	...	...	Neg.		

* Admitted to New Haven Hospital. † Contaminant.

Throughout the febrile period the leukocyte count ranged from 9300 to 16,700 with 74 to 93% neutrophils. Stools were normal, with negative guaiac and microscopic examinations. Cultures of nasopharynx showed the normal flora on two occasions. Roentgen ray of chest showed questionable bronchiectasis at right base.

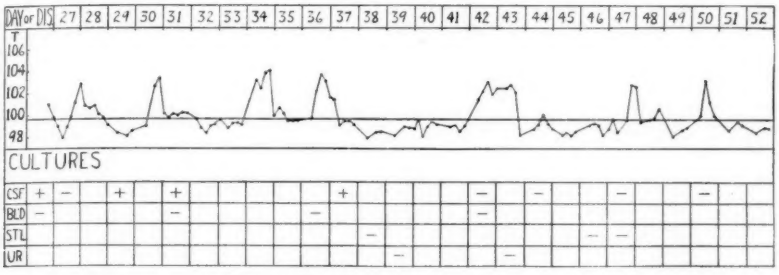

FIG. 1.—Purulent typhoid meningitis with recovery: Case report.

Course. Patient ran an intermittent fever (Fig. 1) for 3½ weeks after admission to the hospital. Febrile periods accompanied by severe headache and increased meningeal irritation usually came on at 3- to 4-day intervals. Treatment was symptomatic. Lumbar punctures were done as often as seemed indicated.

Result. Patient's spinal fluid was sterile after the thirty-seventh day of disease (twelfth day of hospitalization). Thereafter clinical improvement was definite, although fever persisted through the fiftieth day. Patient was discharged from the hospital on May 7, 1936 (sixty-sixth day of disease), apparently in good health. Six months later was again seen and interval history was negative and physical examination revealed the persistence of abnormal physical signs at the right lung base. There were no abnormal neurologic findings. General condition was excellent.

Bacteriology. Results of the bacteriologic investigations of the Gram-negative rod isolated on 4 occasions from the spinal fluid of the patient reported are presented in Tables 2 and 3.

The organism was a Gram-negative rod occurring at first as a highly pleomorphic organism, showing short fat bacilli, "blown up" coccus forms, diplobacilli and long thin rods. After several transplants on standard agar (pH 7.4), the morphology became uniform, the majority of the forms being short Gram-negative rods. On eosin-methylene blue agar, after 48 hours at 37° C., the colonies were raised, smooth, glistening and entire, measuring 1 to 3 mm. in diameter. The colonies had a bluish tinge with reflected light and blue centers with transmitted light. On Krumwiede's triple sugar medium, as well as Russell's medium, an acid butt without gas and an alkaline slant were produced. The organism was motile.

The characteristic biochemical reactions of B. typhosus as presented in Topley and Wilson (1936)[4] were present (Table 2). There is practically complete agreement between the results obtained both in the medical bacteriology laboratory of this hospital and those of the Connecticut State Laboratory* and Topley and Wilson's text.

Serologic evidence presented in Table 3 leaves little doubt of the organism's identity. It will be noted that the organism failed to agglutinate when first isolated, but after several transplants the reaction occurred in significant dilutions.

* To Mr. Friend Lee Mickle, Connecticut State Department of Health, the author is indebted for his interest and coöperation in obtaining the complete bacteriologic data of this organism.

TABLE 2.—BIOCHEMICAL REACTIONS OF SPINAL FLUID ORGANISM.

	New Haven Hospital.	Connecticut State Laboratory.	Topley and Wilson (1936).
Dextrose	A	A	A
Lactose	–	–	–
Mannite	A	A	A
Maltose	A	A	A
Sucrose	–	–	..‡
Salicin	–	–	..
Dextrin	A	..	A
Rhamnose	–	–	–
Raffinose	–	–	..
Inosite	–	–	–
Inulin	–	..	..
Dulcite	–	–	±*
Arabinose	–	A	±
Cellibiose	..	–	..
Xylose	..	–	±
Sorbite	..	A	A
Galactose	..	A	..
Adonite	..	–	..
Citrate	..	–	..
Voges-Proskauer	..	–	..
Methyl red	..	+	..
Nitrate	..	+	..
Indol	..	–	..
Gelatin	..	–	..
Litmus milk	..	Sl. ac.	Ac. or neut.
Lead acetate	..	–	+
Glycerol	..	–	–

± * variable or delayed fermentation. ‡ .. test not done.

TABLE 3.—SEROLOGIC REACTIONS OF SPINAL FLUID ORGANISM.

Test.	Result.
Patient's organism *vs.* typhoid serum (New Haven Hosp.)	–
	1:5000
	1:320
	1:2560
Patient's organism *vs.* typhoid serum (Conn. State Lab.)	1:10240 (H)
	1:10240 (O)
	1:640 (vi)
Patient's organism *vs. B. paratyphosus* A serum.	–
Patient's organism *vs. B. paratyphosus* B serum.	–
Patient's organism *vs. B. abortus* serum	–
Patient's organism *vs.* meningococcus serum	–

Comment. There are several unusual features in this case worthy of mention. Outstanding is the fact that clinical typhoid fever was never present or at least never recognized in this patient. In addition, the onset was fairly typical of meningitis and stiff neck was observed as early as the fourth day of the disease, suggesting that this represents a primary typhoid meningitis. The organism was isolated from the spinal fluid only. Agglutinins for stock strains of B. typhosus or his own organism could never be demonstrated either in blood serum or spinal fluid. Perhaps even more unusual is the fact that the patient recovered.

Summary. A case of purulent typhoid meningitis with recovery is presented.

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INFLUENCE OF SEASON AND CLIMATE ON THE MORTALITY OF THE WHITE AND COLORED POPULATION FROM TUBERCULOSIS AND THE ACUTE RESPIRATORY INFECTIONS.

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If, as is commonly believed, negroes are ill-adapted to withstand the rigors of colder climates, it would seem not improbable that this fact is due in large part to the influence of respiratory diseases. Not only is mortality from these diseases higher in winter than in summer, but there is evidence that it is higher in cold than in warm climates, although the influence of season is much greater than that of latitude. If cold enhances the mortality from respiratory diseases more in negroes than in whites, it might be regarded as playing a principal part in determining the present geographic distribution of the two races.

In studying this question an obvious procedure would be to compare the respiratory death rates of the two races in different climatic areas. In the United States the value of such a comparison, however, is reduced by the fact that northern and southern negroes live under different conditions and differ in education, economic status, age composition, and the admixture of white blood. Besides, the northern negroes are largely urban, whereas southern negroes are mainly rural. Hence it is not evident to what extent the differences in mortality of northern and southern negroes are due to climate and to what extent they result from the various other factors I have mentioned.

For this reason it occurred to me that some pertinent information might be gained by studying the seasonal trend of the respiratory death rate in the two races within the same geographic regions. With the aim of securing a large amount of statistical data on the subject, I have compiled the number of deaths from respiratory diseases and tuberculosis occurring in each month of the year in 9 states: namely, Tennessee, Maryland, North Carolina, South Carolina, Mississippi, Louisiana, Florida, Kentucky, and Virginia. These states were chosen because they have a large negro population and because separate tables for the white and colored inhabitants are available in the volumes on mortality statistics over the entire 10-year period covered, which extended from January 1, 1921,

to December 31, 1930. The area includes approximately one-half of the whole negro population of the United States. Although data are not available for negroes as distinct from other colored races, the colored population of these states consists of over 99% of negroes. In the calculations of monthly death rates the number of deaths in each month was adjusted to a month of constant length. The populations exposed to death in the several months were calculated as of the 15th of each month on the basis of an assumed constant rate of increase during the period.

The study brought out the striking fact that although the respiratory death rate for both races varied greatly with season, the variations were much less in the colored than in the white population. In such a study one may easily be betrayed, on account of variations of disease incidence, combined with variations in the proportions of the two races in different areas. Hence, in order to guard against any statistical fallacy thus arising, I have also compared seasonal fluctuations in mortality in the two races within the limits of individual cities. In the few cities in which sufficient data are available, the month of lowest mortality from lobar pneumonia and bronchopneumonia in both races is July or August. The month of highest mortality tends to occur earlier in the South than in the North. In the cities of the South the most fatal month for respiratory diseases is usually January, as it is for the 9 states investigated, but it is more commonly March in the cities of the North. The death rate increases in September, and more rapidly in October, November, and December. For the sake of comparing the seasonal fluctuations in respiratory death rates in the white and colored populations, I have added the deaths in the 4 months of lowest mortality, usually June, July, August, and September, and have compared these with the 4 months of highest mortality, usually December, January, February, and March. In each of the large cities studied, the differences between summer and winter mortality

TABLE 1.—RATIOS OF WINTER TO SUMMER MORTALITY FROM RESPIRATORY DISEASES IN THE WHITE AND COLORED POPULATIONS OF SELECTED NORTHERN AND SOUTHERN CITIES, 1921–1930, INCLUSIVE.

City.	Lobar pneumonia. White.	Lobar pneumonia. Colored.	Broncho-pneumonia. White.	Broncho-pneumonia. Colored.
Chicago	3.5	2.8	3.2	2.5
New York	3.8	3.6	2.9	2.4
Philadelphia	4.8	3.5	3.5	2.5
Baltimore	5.4	3.6	3.2	2.8
Atlanta	3.6	2.5	4.5	2.4
New Orleans	3.1	2.2	2.2	1.7

from both lobar pneumonia and bronchopneumonia were greater in the white than in the colored population. The evidence that I have been able to secure indicates that the seasonal fluctuations in the respiratory death rate are greater in the whites than in the negroes in rural areas, as well as in cities and in the several states.

The relative fluctuations of the death rates of the two races from respiratory diseases are subject to considerable variation. In New York City the difference in degree of fluctuation is relatively small as compared with that which was found in other cities and states. In Mississippi, a state in which the population is mainly rural, the seasonal fluctuation is about the same in both races, and for lobar and undefined pneumonia is slightly, but perhaps not significantly,

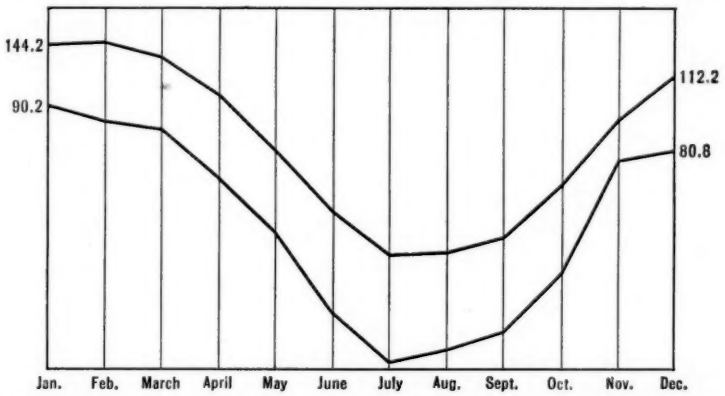

FIG. 1.—Death rates by month from pneumonia (lobar and undefined) in the white and colored population of 9 selected states, 1921–1930. This and the following graphs are drawn to a logarithmic scale in order better to represent changes in mortality rates. Mortality of the colored shown by upper line, that of whites by lower line. Rates per 100,000.

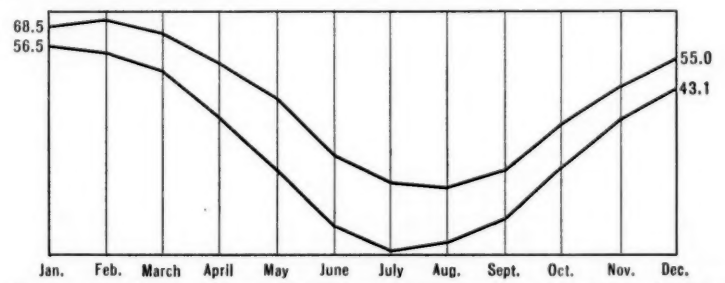

FIG. 2.—Death rates by month from bronchopneumonia in the white and colored population of 9 selected states, 1921–1930. Mortality rates of the colored represented by upper line, that of whites by lower line. Rates per 100,000.

greater for the whites than for the colored population. In Alabama and Georgia, for the period before 1930 in which these states were in the Registration Area, and also Louisiana—states in which the vital statistics of white and colored people might be fairly comparable to those of Mississippi—the whites showed a greater seasonal fluctuation than the colored from both lobar and bronchopneumonia.

There seems to be little relation between the death rate from pneumonia and the degree of its seasonal fluctuation. One finds

marked seasonal fluctuations, as in Baltimore, associated with a high pneumonia death rate, and also marked seasonal fluctuation associated with low pneumonia death rate, as in Mississippi. Possibly the extent of seasonal fluctuation may be influenced by age composition, but in the absence of mortality rates by months in the several age groups it is not possible to secure definite information on this point.

TABLE 2.—DEATHS BY MONTH AND DEATH RATES FROM RESPIRATORY DISEASES IN THE WHITE AND COLORED POPULATION OF 9 SELECTED STATES, 1921–1930.

	Pneumonia, lobar and undefined.				Bronchopneumonia.				Bronchitis.			
	Deaths.		Rates.		Deaths.		Rates.		Deaths.		Rates.	
	W.	C.	W.	C.	W.	C.	W.	C.	W.	C.	W.	C.
January	9938	6582	90.2	144.2	6526	3125	59.3	68.5	786	424	7.14	9.30
February	8799	6700	79.8	146.9	6232	3309	56.5	72.5	806	410	7.31	8.99
March	8339	5983	75.5	131.0	5440	2982	49.3	65.3	722	407	6.54	8.91
April	5717	4462	51.7	97.7	3790	2365	34.3	51.8	552	317	4.99	6.95
May	3812	2971	34.4	65.0	2517	1812	22.7	39.7	395	281	3.56	6.16
June	2044	1819	18.5	39.7	1659	1168	15.0	25.6	298	239	2.69	5.23
July	1408	1320	12.7	28.8	1296	953	11.6	20.9	254	216	2.29	4.73
August	1549	1339	13.9	29.3	1471	922	13.2	20.2	273	217	2.46	4.75
September	1780	1507	16.0	32.9	1764	1050	15.8	22.9	328	223	2.95	4.87
October	2849	2229	26.6	48.6	2623	1510	23.5	33.0	498	282	4.48	6.16
November	5223	3699	58.8	80.8	3797	1994	34.1	43.6	586	317	5.24	6.92
December	7123	5141	63.7	112.2	4818	2518	43.1	55.0	608	327	5.45	7.14

TABLE 3.—DEATHS AND DEATH RATES FROM INFLUENZA AND TUBERCULOSIS IN THE WHITE AND COLORED POPULATIONS OF 9 SELECTED STATES, 1921–1930.

	Influenza.				Pulmonary tuberculosis.				Tuberculosis, other forms.			
	Deaths.		Rates.		Deaths.		Rates.		Deaths.		Rates.	
	W.	C.	W.	C.	W.	C.	W.	C.	W.	C.	W.	C.
January	14,424	6958	130.9	152.5	8821	7557	80.0	165.7	886	697	8.04	15.29
February	10,041	6157	91.1	135.1	9033	8048	81.9	176.4	976	714	9.03	15.65
March	9,663	6122	87.5	134.2	9147	8456	82.8	185.3	1012	768	9.17	16.84
April	5,653	3840	51.1	84.1	8862	8772	80.2	192.1	1038	872	9.39	19.10
May	2,462	1851	22.2	40.6	7702	8615	69.6	188.6	992	942	8.96	20.62
June	1,000	917	9.0	20.0	7348	8154	66.3	178.4	980	897	8.84	19.64
July	602	551	5.4	12.0	6805	7762	61.3	169.8	992	845	8.94	18.44
August	576	411	5.2	9.0	6303	7179	56.7	157.0	878	785	7.90	17.17
September	760	547	6.8	12.0	6005	6371	54.0	139.3	877	703	7.88	15.36
October	1,326	836	11.9	18.2	6218	6528	55.8	142.6	861	704	7.73	15.38
November	2,542	1661	22.8	36.2	6719	6630	60.2	144.8	815	605	7.30	13.21
December	6,225	3430	55.7	74.9	6994	6658	62.6	145.4	809	608	7.24	13.27

In the area and 10-year period investigated, deaths from lobar pneumonia, bronchopneumonia, and bronchitis reached their highest rates in January or February, and their lowest rates in July or August. For bronchitis the ratio of deaths in the 4 months of lowest mortality to deaths in the 4 months of highest mortality is nearly 1:3 in the whites, and slightly less than 1:2 in the colored race (Table 2).

In the years studied, influenza, like other respiratory infections, is much more fatal in winter than in summer. Mortality in the cold months is about 9 times as high as in warm months in the

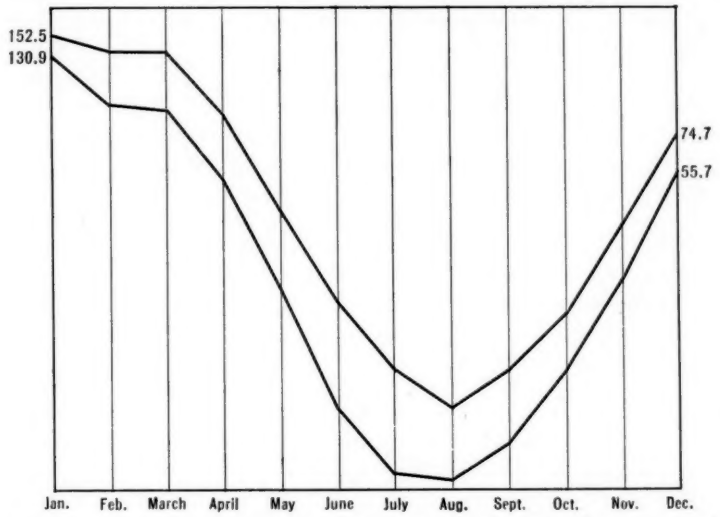

FIG. 3.—Death rates by month from influenza in the white and colored population of 9 selected states, 1921–1930. Mortality rates of the colored shown by upper line, that of whites by lower line. Rates per 100,000.

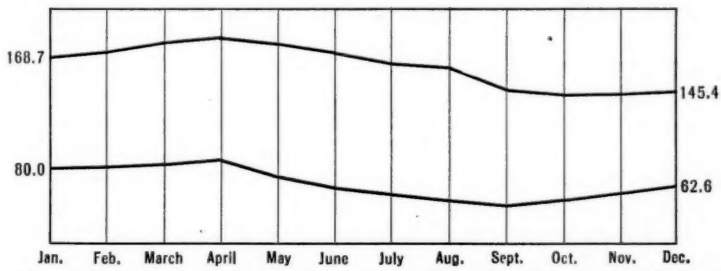

FIG. 4.—Death rates by month from pulmonary tuberculosis in the white and colored population of 9 selected states. Mortality of the colored shown by upper line, that of whites by lower line. Rates per 100,000.

colored, and over 13 times as high in the white race. The highest mortality for both races occurred in January, and the lowest in August. It is doubtful if this month of maximum mortality will be found to be of general occurrence. There is much variation in severity from year to year in all of the acute respiratory infections, but influenza is more fitful in its visitations than any of the others.

The seasonal variations in mortality from pulmonary tuberculosis (Table 3) are in several respects parallel with those of the acute respiratory infections, but they show some differences which place

tuberculosis in a somewhat different category. The highest mortality rates are scarcely more than 50% higher than the lowest ones, instead of several times as high, as in the pneumonias. The fluctuations in mortality from tuberculosis in the colored populations are closely parallel to those of the white and show about the same relative degree of seasonal change, although the death rate is a little over twice as high as in the white race. That the wave of highest mortality from tuberculosis which comes in April lags behind that of the acute respiratory infections may be due to the fact that people usually die from the latter diseases soon after they contract them, and that people are less apt to contract them in warm weather. Although tuberculous patients do not have so plentiful a supply of fresh air in winter as in summer, the higher mortality from tuberculosis in the colder months may be in part due to the acute respiratory infections which afford the immediate occasion of death. Many such deaths would be reported, and properly so, as due to tuberculosis. The seasonal distribution of "other forms of tuberculosis" differs from that of the respiratory forms in that the highest mortality in both the white and the colored populations occurs in the spring and early summer, and the lowest ratio in the fall and early winter.

Our data indicating that in the colored population mortality from respiratory diseases fluctuates less with the seasons than that of the white population might dispose one to infer that higher latitudes, while increasing the respiratory death rate in both whites and colored people, would lead to a greater relative increase in the mortality of the colored race. One cannot, however, safely argue from the effects of seasonal change to the effects of change of latitude. The lower seasonal fluctuations in mortality of the colored people may be due to the fact that for some reasons negroes are much more apt than whites to die from respiratory diseases in summer. I suspect that this is the case, but whatever may be the character or the course of the seasonal change in mortality from respiratory diseases in the two races, the change from rural life in the South to urban life in the North affects negroes very much more unfavorably than white people. Between the crude mortality rates from pneumonia in the rural South and in the rural North there is roughly an average difference of from 30 to 75% for the whites, and from 200 to 300% for the colored population. Possibly the destructive influence of negro migration into the North is due more to the fact that the migration is urban than that it involves life in a northern climate.

For light on this subject one would naturally turn to a comparison of the respiratory death rates of northern and southern urban negroes, but such a comparison reveals many irregularities and little relation to latitude. The death rate from pneumonia is high in the colored population of Atlanta, Chattanooga, Dallas, Baltimore, Richmond, and Washington, D. C. Relatively low rates

from pneumonia occur in the colored inhabitants of Philadelphia, Chicago, and, especially, Gary. These variations, however, may be largely caused by differences in age composition, educational status, and the frequency of climatic changes in different cities.

TABLE 4.—PERCENTAGES OF TOTAL DEATHS DUE TO PNEUMONIA AND DEATH RATES PER 100,000 IN THE WHITE AND COLORED POPULATION OF RURAL AND URBAN AREAS OF SELECTED STATES, 1921–1929.

State.	Percentage of pneumonia to total mortality.				Mortality per 100,000.			
	White.		Colored.		White.		Colored.	
	Urban.	Rural.	Urban.	Rural.	Urban.	Rural.	Urban.	Rural.
Illinois	7.80	7.58	12.12	7.22	82.7	63.4	216.5	222.5
New York	9.63	6.75	15.65	9.44	95.2	68.2	264.7	138.8
Pennsylvania	10.46	9.07	17.98	11.02	115.3	88.1	257.2	204.1
Ohio	7.83	6.84	14.23	7.53	113.9	84.8	287.7	160.0
Maryland	9.70	6.97	15.40	8.39	134.8	73.3	347.0	146.3
Virginia	5.96	6.42	10.05	6.53	76.8	64.9	232.1	112.6
South Carolina	5.89	7.16	7.57	6.99	102.0	61.5	229.6	99.4
Mississippi	6.08	7.24	6.50	6.27	121.9	66.4	184.0	78.9
Louisiana	6.08	7.77	9.01	7.06	83.3	48.9	209.2	83.7

But notwithstanding irregularities due to causes other than climate, the crude mortality rates from the acute respiratory infections are in general higher in northern than in southern urban areas. This is indicated by Table 4, which embodies data from a few typical southern states and some states of the North having a large negro population. The ratios of deaths from pneumonia to total deaths are based on deaths in urban areas from 1921 to 1929, and the death rates per 100,000 are calculated for 1929, which are fairly typical of those for the other years. The data give reasonable support to the following conclusions as to the relation of mortality rates from pneumonia:

For the rural population death rates from pneumonia in the North exceed those in the South very much more in the colored than in the white population. The data are doubtless influenced by the fact that in the North the proportion of colored inhabitants other than negroes is much greater than in the South, but in the states studied the proportion of other colored is in no case as great as 25%.

In the colored population of the South, urban and rural mortality rates differ much more than in whites.

In the colored population of the North, rural and urban mortality rates from pneumonia differ much less than in the South. Pneumonia rates in southern rural negroes are relatively low.

In the white population of the North death rates from pneumonia are probably enhanced more than in the South on account of the higher proportion of foreign-born inhabitants, among whom mortality from pneumonia is relatively high.

The rural white population, which differs less between North and South than the urban whites or either the urban or rural negroes, shows little change in pneumonia mortality in relation to latitude.

I have calculated the pneumonia death rates of the white rural population in several states, both North and South. In 1932, for example, these rates per 100,000 inhabitants were as follows in a few typical states of the South: Alabama, 54; Florida, 39.6; Georgia, 58.5; Louisiana, 48.9; Mississippi, 42.9; North Carolina, 64.7; South Carolina, 64.9; Virginia, 61.5. In a sample of northern states the rates were: Illinois, 66.3; Pennsylvania, 71.2; New York, 77.5; Michigan, 64.9; Ohio, 68.6; Massachusetts, 74; Wisconsin, 64.8. A calculation of the mortality rates for pulmonary tuberculosis in the rural white population in the same states for 1932 gives the following data: Alabama, 39.8; Florida, 38.9; Georgia, 30.2; Louisiana, 26.5; Mississippi, 35.1; North Carolina, 38.7; South Carolina, 26.2; Virginia, 56.8; Illinois, 59.6; Pennsylvania, 54.2; New York, 74.6; Massachusetts, 113.3; Michigan, 47.1; Ohio, 46.8; Wisconsin, 47. Tuberculosis, like pneumonia, is apparently more fatal to the rural white population in the North than in the South. This conclusion is, of course, what one would expect in the light of seasonal fluctuation in mortality from these diseases.

The migration of negroes from the rural South to the cities of the North, where they become crowded together in limited spaces that favor the spread of all sorts of infections to which they have previously built up little resistance, has resulted in many deaths. Not improbably the negro will in time acquire a greater measure of immunity to these infections, as other races have done. In fact, there is evidence that the American negro has developed a partial immunity to tuberculosis which renders him less apt to succumb than are colored races that have not been in frequent contact with this disease. But even if the negro develops a degree of resistance to pulmonary infections comparable to that of the whites, he will probably continue to be handicapped by his inferior status for many years. Whether or not the genetic constitution of the negro predisposes him to fall a victim to respiratory diseases, these diseases will nevertheless continue to constitute selective agents acting on the basis of racial heredity. The skin color and other anthropologic characters that cause negroes to be identified as such and lead to their segregation in unfavorable surroundings or their employment in less remunerative occupations constitute indirect causes of selective mortality. These anthropologic characters may not have the slightest direct connection with death from any cause whatever, but if they have an indirect influence, even through the effects of poverty, ignorance, or race prejudice, they may lead to the selective elimination of their possessors. For these reasons, if for no others, respiratory disease will continue to be more fatal to negroes, so long as the social and economic relations of the races remain essentially as they are at the present time.

Another circumstance that increases the racially destructive effect of respiratory disease among the negroes is their relatively high death rates from these diseases in early adolescent and middle periods of life. From the standpoint of racial survival it matters relatively little what happens to people after they have passed the reproductive period. The age distribution of deaths from both tuberculosis and the acute respiratory infections is much more of a handicap to natural increase in negroes than in whites, and since cities, both North and South, attract negroes in the adolescent and middle age periods, their racially destructive influence is all the more potent.

Summary. Seasonal fluctuations in mortality from tuberculosis and the acute respiratory infections were studied in the white and colored populations of 9 states in which deaths from different diseases were classified by month and by color over a 10-year period from January 1, 1921, to December 31, 1930.

For the pneumonias and bronchitis, the lowest mortality for both races occurred in July or August, and the highest in January or February.

The extent of seasonal fluctuations in mortality was greater from lobar (and undefined) pneumonia than for bronchopneumonia in both the white and colored populations.

The seasonal fluctuations in mortality from influenza were greater than those in mortality from the pneumonias.

Mortality from tuberculosis varies much less with seasons than mortality from the acute respiratory infections.

The highest and lowest mortality from pulmonary tuberculosis occurred about 2 months later than the highest and the lowest mortality from the pneumonias and bronchitis.

The seasonal fluctuations of mortality from lobar pneumonia and bronchopneumonia were significantly less in the colored than in the white population, not only in the whole area studied but also in the several states and in each of 6 large cities, both North and South. For the entire area mortality from influenza and bronchitis, and, to a less extent, from pulmonary tuberculosis, showed a greater seasonal fluctuation in the white than in the colored population.

For all races death rates from respiratory diseases are higher in cities than in rural areas under comparable climatic conditions.

Differences in respiratory death rate between urban and rural areas of the South are very much greater in the colored than in the white population.

Although death rates from pneumonia in the colored population are higher in some large cities of the South than in most large cities of the North, these rates are in general higher in northern than in southern cities.

The mortality from pneumonia and tuberculosis in the colored people of the North is nearly as high in rural as in urban areas. Differences in mortality from respiratory diseases between the rural

South and the urban North are very much greater in the colored than in the white population.

In their effects on mortality from tuberculosis and acute respiraratory infections cities are relatively much more destructive to negroes than to whites. Under present conditions mortality from respiratory disease acts as a powerful check to the natural increase of the negro race in northern latitudes.

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ESSENTIAL HYPERTENSION IN THE NEGRO.

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All studies on heart disease in the American negro,[5, 6a, 9, 12a, b, 13, 16] including negroes residing in Jamaica,[14] stress the predominance of hypertension as an etiologic factor. There is also reported a greater incidence of hypertension in the negro than in the white race. In a group of 1000 negro male factory workers employed in the Cincinnati metropolitan area, 249 had hypertension; whereas of 1000 white male workers in the same community and approximately the same age distribution, only 91 had hypertension.[2] Adams[1] found the blood pressure of apparently healthy negro industrial workers to be higher than that of white employees. The pressures after 40 years of age advanced more rapidly in the colored than in the white race. Alvarez and Stanley[3] found that the blood pressure rises more rapidly with age in negro than in white prisoners.

The present report is a study of the manifestations of essential hypertension in the negro as observed at the Louisville City Hospital.

In consecutive order, there was analyzed the records of 1198 negro patients admitted to the hospital with an elevated blood pressure which was considered to be essential in type. In most instances, the patients were admitted to the wards for some complication of the hypertension. In the remainder, the elevated blood pressure was found in the course of a routine physical examination. Only adults over 20 years old were included, since few children are admitted to this institution. These observations are compared with 989 white patients with essential hypertension admitted to the hospital during the same period.

TABLE 1.—AGE AND SEX INCIDENCE OF ESSENTIAL HYPERTENSION IN NEGRO CONTRASTED WITH WHITE RACE AND CONTROL GROUPS.

Age.	HYPERTENSION.								CONTROL.							
	Negro (1198 cases).				White (989 cases).				Negro (1666 cases).				White (2724 cases).			
	M.	F.	Total.	Total, %.	M.	F.	Total.	Total, %.	M.	F.	Total.	Total, %.	M.	F.	Total.	Total, %.
20–24	..	1	1	0.1	..	3	3	0.3	101	140	241	14.4	157	284	441	16.2
25–29	8	2	10	0.8	..	1	1	0.1	110	140	250	15.0	139	264	403	14.7
30–34	10	23	33	2.8	4	6	10	1.1	92	112	204	12.3	159	133	292	10 7
35–39	28	49	77	6.4	8	13	21	2.1	151	134	285	17.1	144	146	290	10.6
40–44	58	65	123	10.2	15	17	32	3.2	87	78	165	9.9	105	102	207	7.6
45–49	73	97	170	14.2	38	41	79	7.9	104	73	177	10.7	131	56	187	6.8
50–54	107	95	202	16.8	67	42	109	11.1	58	45	103	6.2	125	99	224	8.2
55–59	74	71	145	12.1	60	47	107	10.9	37	20	57	3.4	112	73	185	6.8
60–64	87	55	142	11.8	102	53	155	15.7	36	41	77	4.6	103	35	138	5.1
65–69	81	49	130	10.9	97	69	166	16.6	41	6	47	2.8	105	35	140	5.2
70–74	51	31	82	6.9	92	52	144	14.5	21	10	31	1.8	70	32	102	3.7
75–79	31	15	46	3.9	58	36	94	9.5	11	2	13	0.8	42	15	57	2.1
80–84	12	7	19	1.5	27	16	43	4.4	7	4	11	0.7	27	12	39	1.1
85–89	9	6	15	1.3	9	10	19	1.1	1	1	2	0.1	9	7	16	0.7
90+	..	3	3	0.3	5	1	6	0.6	3	..	3	0.2	....	3	3	0.1
	629	569	1198	100.0	582	407	989	100.0	860	860	1666	100.0	1428	1296	2724	100.0

Age and Sex Incidence. Table 1 shows the age and sex distribution of the cases which occurred in each 5-year period contrasted with the white patients, along with 4390 non-hypertensive individuals (1666 negro and 2724 white), admitted to the hospital for a 6-month period (July through December, 1936). There were 629 men and 569 women. The greatest incidence (16.8%) occurred in the 50 to 54-year age period. A majority of the cases (76.0%) were from 40 to 70 years. In the white race, the maximum number of cases were to be found in the 60-year age group, and 78.3% were from 50 to 80 years of age. Below the fortieth year, there was a much higher incidence than in the white race, 10.1% in contrast with 3.6%. In the control patients, 58.8% of the negroes and 52.2% of the whites were less than 40 years of age. From this it is evident that the greater incidence of hypertension in the negro in the younger age groups was not the result of admission to the hospital of younger negro patients.

An analysis of the sex incidence with reference to age shows that hypertension manifests itself earlier in the female than in the male, there being 41.6% of the female cases before the fiftieth year and only 28% of the male patients. The percentage age frequency curve (Fig. 1) shows that the curve for the women reaches a peak

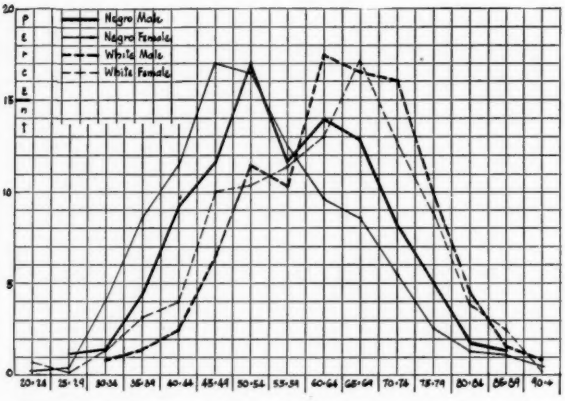

FIG. 1.—Percentage frequency curves in five-year age groups of hypertension in negro and white males and females.

5 years earlier than the men. The per cent incidence of the total number of each sex in the fourth decade was twice as great in the women as in the men. In the women 57.6% of the cases were from 40 to 60 years of age; in the men 55.5% were in the 50- to 70-year groups. These conclusions apply likewise to the white patients. This earlier incidence of hypertension in the negro female is only slightly influenced by the greater frequency with which young females enter the hospital. Thus 46.6% of 1382 control cases below 50 years of age were men, and 53.4% were women.

The relative incidence of the sexes was calculated on the theoretical basis that equal numbers of each sex were admitted to the hospital.[10] With this method of determination it is found that there was practically an equal distribution of the two sexes, 50.9% occurring in men and 49.1% in women. On a like basis of calculation the sex distribution in the white patients showed a slight preponderance of women, 56.5% and 43.4% in the female and male cases respectively. These observations are similar to those of Schwab and Schulze[12a,b] in negroes of Texas with hypertensive heart disease except that they found this type of heart disease to occur 1½ times more often in the negro female than in the negro male. Others[9,13] have also reported that hypertensive heart disease reaches its point of greatest frequency a decade earlier in the negro than in the white race.

Major Complications. The major complication, namely cardiac, cerebral (hemorrhage, thrombosis, embolism) and renal were

especially analyzed. Only patients with uremia were placed in the renal group. Table 2 is the distribution of these chief clinical types

TABLE 2.—ANALYSIS OF MAJOR COMPLICATIONS.

	Negro (1198 cases).					White (989 cases).				
	M.	F.	Total.	Total cases, %.	Cases with complications, %.	M.	F.	Total.	Total cases, %.	Cases with complications, %.
Cardiac (uncomplicated)	366	238	604	50.4	....	261	163	424	42.9	
Cardiac + cerebral . .	10	14	24	2.0	....	7	7	14	1.4	
Cardiac + uremia . .	40	26	66	5.5	....	25	7	32	3.2	
Cardiac + cerebral + uremia	2	..	2	0.2	....	..	1	1	0.1	
CARDIAC . . .	418	278	696	...	68.4	293	178	471	...	66.0
Cerebral (uncomplicated)	97	86	183	15.2	....	110	48	158	16.0	
Cerebral + uremia . .	8	7	15	1.2	....	8	5	13	1.3	
CEREBRAL . .	117	107	224	...	22.0	125	61	186	...	26.0
Uremia (uncomplicated)	8	6	14	1.2	....	5	7	12	1.3	
UREMIA . . .	58	39	97	...	9.6	38	20	58	...	8.0
Total	531	377	908	75.7	100.0	416	238	654	66.2	100.0

compared with the white patients. One or more of these complications occurred in 75.7% of the cases in contrast to 66.2% in the white patients. They were present in 84.5% of the 629 men and 66.3% of the 569 women. Similarly, more white male patients suffered these complications, 71.5% and 58.5% in the male and female sexes respectively. In both races it was rare to find a patient in uremia without coincident heart failure, or a cerebral vascular accident. The cardiac and cerebral groups were usually distinct types. Of these major complications, myocardial insufficiency accounted for 68.4%, cerebral vascular accidents occurred in 22.0% of the patients, and 9.6% had uremia. There was practically a similar distribution among the white cases. The individual complications occurred with an approximately equal frequency in the sexes of both races. Table 3 is the percentage age frequency with which the cardiac, cerebral and renal cases occurred in each 10-year age period. The point of greatest frequency reaches

TABLE 3.—PERCENTAGE AGE FREQUENCY OF MAJOR COMPLICATIONS.

	Negro.			White.		
Age.	Cardiac.	Cerebral.	Uremia.	Cardiac.	Cerebral.	Uremia.
20–29	0.7	0.9	....	0.2	....	....
30–39	8.0	4.5	8.2	3.2	2.7	3.5
40–49	24.6	24.1	30.9	9.1	12.8	12.0
50–59	30.2	33.5	28.9	21.6	20.4	25.9
60–69	23.9	20.5	18.6	35.3	34.9	31.0
70–79	9.8	13.8	12.3	22.7	24.3	19.0
80+	2.8	2.7	1.0	7.8	4.8	8.6

a peak 10 years earlier in the negro than in the white patients. Uremia in both races occurred more frequently in the younger age groups. Bell and Clawson[4] found that the average age in the renal was lower than that in the cardiac and encephalic types of essential hypertension.

Angina Pectoris. A classical history of angina pectoris was obtained in only 6 cases (0.5%). There was a similar low incidence in the white patients, 1.5%. Numerous authors have commented on the infrequency with which angina pectoris is encountered in negroes. In this institution, cardiac pain is rarely found in a negro even with clinical and electrocardiographic evidence of coronary artery sclerosis. Roberts[11] attributes it to the lack of mental stress and strain in the negro. Schwab and Schulze[12b] believe it is due to an inherent difference in the sensitivity of the nervous systems in the white and negro. Neither of these explanations is entirely sufficient, since angina pectoris is also infrequent in the white patients admitted to this institution. In articles on angina pectoris there are numerous comments on the comparative infrequency with which it is encountered in patients confined in charitable institutions. Hamman[7] believes this is due to their low level of intelligence. It is of interest that the more unmistakable histories of angina were obtained in the white patients who were above the intellectual and social level of the average patient admitted to the wards of this municipal hospital. The economic depression necessitated their admission to a free institution. Multiple factors are responsible for the low incidence of angina pectoris in the hospitalized negro. 1. Lack of intellectual ability fully to interpret and describe the sensation of cardiac pain; 2. The distress of myocardial, cerebral or renal failure symptoms can obscure all history of angina pectoris; 3. Uncomplicated anginal type of heart failure is usually the complaint of an ambulatory patient.

Auricular Fibrillation. This was present in 83 cases (7.0%). The white patients had a slightly higher incidence (10.6%). Table 4

TABLE 4.—AGE AND SEX INCIDENCE OF AURICULAR FIBRILLATION.

	Negro.				White.			
Age.	Male.	Female.	Total.	Total, %.	Male.	Female.	Total.	Total, %.
40–49	4	5	9	10.8	1	2	3	2.9
50–59	10	9	19	22.9	12	8	20	19.0
60–69	20	11	31	37.4	24	11	35	33.3
70–79	13	6	19	22.9	26	13	39	37.2
80–89	4	1	5	6.0	4	3	7	6.6
90+	..	..	..	...	1	..	1	1.0
Total	51	32	83	100.0	68	37	105	100.0

gives the age and sex incidence. While the youngest case in both races was 42 years of age, there was a greater incidence a decade earlier in the negro than in the white patients. The male sex predominated in both races. Over 80% of the cases of auricular fibrillation were associated with congestive heart failure. Flaxman[6b]

found that 9.8% of colored and 32.3% of white patients with hypertensive heart disease had auricular fibrillation.

Syphilis. The incidence in this hospital of syphilis in the negro with primary hypertension has been reported.[8] Of 369 negroes 112 (30.4%) had a serum reaction positive for syphilis; whereas only 9.5% of 297 whites had serologic evidence of the infection. In a control group, 32.6% of the negroes and 18.8% of the whites had a positive Wassermann.

Diabetes. Diabetes of varying severity was present in 45 patients of each race, 3.7% in the negro and 4.5% in the white. The number of cases of each sex was as follows: negro males, 10; negro females, 35; white males, 15; white females, 30. There was no case in the white race below the age of 40, but there were 3 negro females in the fourth decade. Congestive failure was present in 11 of the negro and 6 of the white diabetics. A cerebral vascular accident occurred in 3 patients of each race. Bell and Clawson[4] state that 5.5% of hypertensive persons over 50 years have diabetes. White[15] found that 1.5% of his cases of hypertensive heart disease had coincident diabetes.

Summary. 1. A study is presented of the manifestations of essential hypertension in 1198 negroes admitted to the Louisville City Hospital, compared with 989 white hypertensives admitted to the wards during the same period.

2. Hypertension occurred a decade earlier in the negro than in the white race. In the negro, 10.1% of the cases were below the fortieth year in contrast with 3.6% in the whites.

3. The percentage age frequency curve reaches a peak 5 years earlier in women than in men. This applies likewise to the white patients.

4. There was an equal distribution of the sexes. The white hypertensives showed a slight preponderance of women.

5. One or more of the major complications of hypertension—cardiac, cerebral and renal—occurred in 75.7% of the cases in contrast to 66.2% in the white patients. In both races, more male than female patients suffered these complications.

6. Myocardial insufficiency accounted for 68.4% of these major complications, cerebral vascular accidents occurred in 22.0% of the patients and 9.6% had uremia. There was practically a similar distribution among the white cases.

7. Individual complications occurred with an approximately equal frequency in the sexes of both races.

8. The percentage age frequency curve of the cardiac, cerebral and renal cases reaches a peak 10 years earlier in the negro than in the white.

9. Angina pectoris was relatively infrequent in both negro and white.

10. Auricular fibrillation had a slightly higher incidence in the white race.

11. The incidence of syphilis was no greater than in non-hypertensives. This applies to both blacks and whites.

12. Diabetes was present in 3.7% and 4.5% of the negro and white cases respectively.

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OBSERVATIONS ON THE ETIOLOGY OF THE TOXEMIAS OF PREGNANCY.

III. THE LACK OF INFLUENCE OF VITAMIN B (B_1) ON WATER RETENTION IN THE TOXEMIAS OF PREGNANCY.*

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THE physiologic strain of childbearing requires dietary factors to be increased over the standard requirements for women. During pregnancy, various conditions favoring nutritional instability are apt to arise, such as alteration in the gastro-intestinal tract secretions, vomiting and perverted appetite. Thus during pregnancy it is not unusual to see the development of nutritional deficiency disorders such as hypochromic and macrocytic anemia, hypoproteinemia, polyneuritis, and other distinctive vitamin and mineral deficiency syndromes.

Recent studies by Elsom,[2] Weiss and Wilkins[5] and others have indicated that a deficiency of vitamin B_1 may result in water retention irrespective of the level of the plasma proteins and venous pressure.

The importance of water retention and its relation to hypoproteinemia in the true toxemias of pregnancy have been pointed out in the preceding papers of this series.[4a,b] It was shown[4a] that the administration of a diet containing 260 gm. of protein daily

* This study was aided in part by a grant from the William W. Wellington Memorial Research Fund of the Harvard Medical School.

and the parenteral injection daily of 750 Sherman units of vitamin B_1 and 5 cc. of a solution of liver extract which was derived from 25 gm. of liver and was rich in other portions of the vitamin B complex to 10 pregnant women resulted in striking losses of body weight and the disappearance of edema. Each of these women had marked water retention associated with hypoproteinemia. In 6 other pregnant women, however,[4b] the same effects were obtained with the high-protein diet alone. However, since such a diet is in itself relatively rich in the vitamin B complex, it remained possible that the effects secured were the result not of the protein as such but of its vitamin B_1 content.

Methods. In order to decide this point 3 women in the last trimester of pregnancy were selected for study, each of whom presented suggestive evidence of vitamin B deficiency. Each had generalized edema of severe grade, and each had been on a low-protein diet throughout pregnancy. The first 2 patients complained of numbness and tingling of the extremities. These symptoms were consistent with an early stage of polyneuritis, but objective evidence for this was lacking. The third had had persistent vomiting for 6 months. The plasma protein levels of the 3 women were such that the calculated oncotic pressures[6] were 195, 195, and 243 mm. of water, respectively. The venous pressures respectively were 11, 11, and 9 cm. of water.[3] The 3 patients had gained during pregnancy 35, 53, and 23 pounds, respectively. On admission to the hospital, their blood pressures were 136 systolic and 90 diastolic, 184 systolic and 100 diastolic, and 160 systolic and 104 diastolic, respectively. Albuminuria was present in each.

Each patient was ambulatory on the hospital ward. The usual house diets were supplied. No restriction of salts or fluids and no purgation were employed. Commencing on the fourth day, each received by intramuscular injection daily for 4 days 20 mg. of synthetic crystalline vitamin B_1* (at least 8000 Sherman units) and 5 cc. of a solution of liver extract* derived from 25 gm. of liver (fraction G of Cohn, Minot, *et al.*[1] According to Weiss and Wilkins,[5] this amount of vitamin B_1 produces a marked and prompt loss of weight in patients with edema due to vitamin B_1 deficiency.

Results. No significant change in edema or weight occurred in any patient during a period of 1 week beginning with the first day of administration of the vitamin. The arterial blood pressures and the quantitative output of albumin in the urine were likewise unaltered. Symptoms remained unchanged.

As to control for these observations it may be noted that 6 pregnant women with a similar condition given a high-protein diet[4b] showed a weight loss in 1 week's time of 2.9 to 4.1% of their original weight.

Discussion. The data presented offer no evidence for the belief that the water retention of pregnancy toxemias depends on a deficiency of either vitamin B_1 or the other components of the B complex found in liver fraction G of Cohn, Minot, *et al.* It is of course possible that vitamin B_1 may influence the absorption or assimilation of protein foods or the manufacture of plasma protein. Such a possibility is not excluded by these data.

Further evidence that the plasma protein level is the significant factor in determining the degree of water retention in pregnancy

* Kindly supplied by Eli Lilly & Co., Indianapolis.

may be deduced from certain observations, the details of which have been previously reported.[4b] Briefly, after suitable control periods, 20 women in the last trimester of pregnancy with varying plasma protein levels were given sodium (6.3 gm. calculated as Na) chloride or bicarbonate daily. The degree of water retention, as evidence by the percentage gain in body weight after 3 days, has been plotted against the calculated plasma oncotic pressure in Chart I. It is apparent that within limits of error the degree of water retention is inversely proportional to the calculated plasma oncotic pressure.

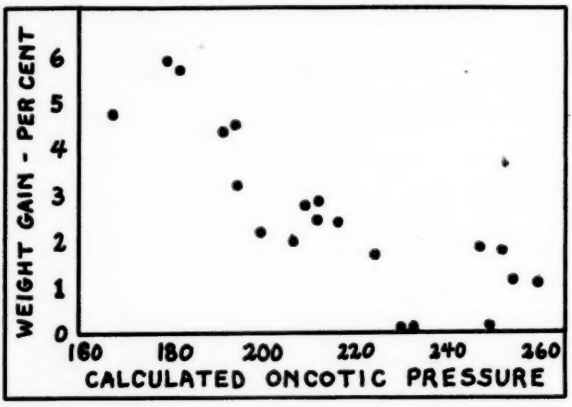

CHART I.—Percentage weight gain in 3 days following the administration of sodium salts to 20 pregnant women plotted against the calculated plasma oncotic pressure in millimeters of water.

Summary and Conclusions. 1. No evidence has been obtained that a deficiency of vitamin B_1 plays a rôle in water retention in pregnancy toxemias.

2. There is an excellent correlation between the level of the colloid osmotic pressure of the plasma proteins and the degree of water retention which may be induced by the administration of sodium salts to pregnant women.

3. Water retention in the toxemias of pregnancy is conditioned chiefly by the level of the plasma proteins.

The writer is indebted to the visiting surgeons and house staff of the Obstetrical Service of the Boston City Hospital for their coöperation which made this study possible. Miss Margaret A. Adams performed the chemical determinations reported in this paper.

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THE BASAL METABOLIC RATE OF CHILDREN WITH SYDENHAM'S CHOREA.

REPORT OF 42 PATIENTS

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SOMETIME ago we observed a young girl who had an irregular tremor, a tachycardia, a soft systolic murmur over the apex of her heart, a moderate pyrexia and a slight loss in weight. It was difficult at the bedside to distinguish between an acute chorea and a mild thyrotoxicosis. The basal metabolic rate was measured in an effort to establish the diagnosis. It was slightly elevated. A review of the standard texts on metabolism and pediatrics[2,5,7,8,10–12,14,16,19] failed to disclose any statement concerning the effect of chorea on basal metabolism.

As it was not unlikely that there had been other cases where the same confusion existed and knowledge of the metabolic rate in chorea would have given additional information of this little understood disease, 42 ambulatory patients were selected from our cardiac follow-up clinic for study. Basal metabolic rates were measured during an acute attack of Sydenham chorea. Twenty had the test quite early in the disease, before the involuntary twitchings were too severe to interfere with the readings. On a number of occasions metabolic estimations were attempted during the height of the disease; but it was impossible to get satisfactory graphs. The 22 others were given basal metabolic tests as soon after the acute phase of the disease had subsided as accurate determinations could be made. In this way, it was believed that any changes in metabolic rate that chorea might induce would be evident either at the beginning or end of the disease.

All readings were made early in the morning during the post-absorptive period. Nearly three-fourths of the group (29) were tested by the Jones metabolometer, the remainder by the Sanborn machine. Calculations were made using the standard tables for children. In those children who ran a slight fever, for each degree of Fahrenheit rise in temperature, 7.3% was deducted. All recorded results have been corrected for pyrexia.

The ages of the children varied from 6 to 14 years; 25 were girls and 17 were boys; 39 were white and 3 were colored. Fifteen had no evidence of cardiac damage, 16 had early mitral stenosis and 11 had a developed mitral stenosis. Of the latter group, 2 followed scarlet fever, 2 had adhesive pericarditis and 2 had free aortic insufficiency in addition to their mitral valve damage.

Basal metabolic rates varied from −24% to +15% with a median at −4.3%. If this average is accepted as the zero point and the

conventional 21% range used, the "normal range" for our series would extend from −14% to +6%. This range agrees well with the findings of Jenkins[13] who found the zero point of −7% in a series of 1126 normal men and 2994 women of the same city. Thirty-one children with chorea (74% of our series) had basal metabolic rates that fell within this "normal range." Five readings were above the upper normal limit viz., +15%, +13, +13, +10 and +7% while 5 were below the lower normal limit or −15, −17, −19, −20 and −24%. This spread is in keeping with the ranges observed in many large series,[15,20] as Talbot *et al.*, found practically 95% of all their measurements were between −20.3 and +25.5%.

In 4 patients we were fortunate in measuring the basal metabolic rates both early and late in the disease. E. W. had −15% early in the disease, −15% a year later and again early in another mild attack of chorea, and −20% several months after the latter attack had subsided. The rates of the other three varied from +15, +6, and −4% early in the disease to +10, −8 and −11% after it had subsided. No exact correlation between the rates early in the disease and those taken later could be made, however, it appeared in general that the basal metabolism was slightly lower after the disease began to wane. Neither did the severity of the disease affect the metabolic rate. Patients were arbitrarily classified as mild, moderate and severe on the basis of their muscular activity, fever, and exhaustion. Careful analysis of these groups failed to show any appreciable difference between groups as all classes showed a similar range of metabolic rates (Fig. 1).

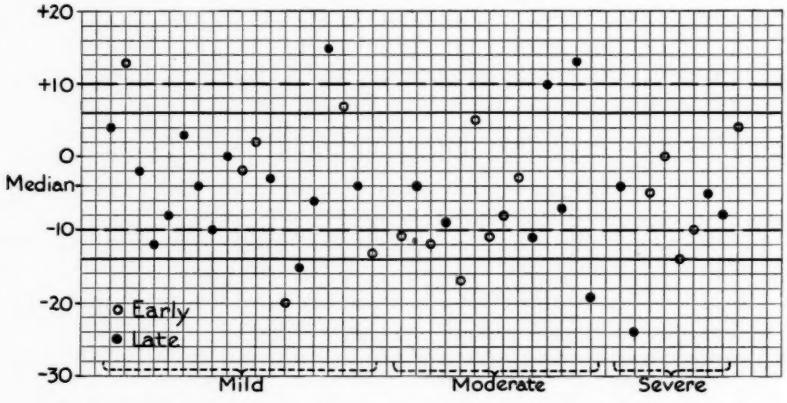

FIG. 1.—Graph showing the distribution of the basal metabolic rates of 42 children with Sydenham's chorea.

Discussion. An extended search of the literature disclosed several references concerning basal metabolism in chorea. Paulian, Padéano and Avicesco[18] (1927) concluded from a study of 3 young girls that

chorea greatly reduced the metabolic rate. Two years later Parhon and Ornstein[17] reported the changes of metabolic rate of 7 patients: in 5 it varied from −3 to +8%, and in a sixth it was +24%, while the seventh patient had a chronic Huntington chorea. The subject was more carefully studied by Warner[21] in 1930. He examined 5 children both in the active and recovered phase of chorea, who showed neither pyrexia nor enlargement of the thyroid gland. The rates were within normal range, except one a +32.7% in a severe chorea. Gerstley[9] classified the basal metabolic rates of choreic children in two groups; averaging between +2 and +4% and averaging between +12 and +14%. Unfortunately, he offers no explanation for these two groups.

The muscular twitchings of chorea have been the subject of much speculation. It was formerly believed to have been a peculiar or partial contraction of the muscles. The subject was critically studied by Stanley Cobb.[6] By means of non-polarizable electrodes he transmitted the action currents of the affected muscles to a string galavanometer and recorded them on moving paper, a procedure similar to electrocardiography. Action currents of voluntary muscular contraction showed very little qualitative difference from the twitchings of chorea.

Increase of basal metabolic activity after muscular exercise has been known for a long time. As early as 1898 Rubner and Huebner observed that a restless infant produced more heat than a quiet one. Benedict and Talbot[4] devised a special apparatus which enabled them to record movements of the bed as well as heat production. They found that very small infants who were normally active had 25% more heat production than the normal basal rates gave. Similarly Benedict and Carpenter[3] demonstrated that a normal man used 17% more oxygen when standing than when seated. The seemingly slight muscular activity needed for standing moderately increased the metabolic rate. From this it has been suggested that the tremor of exophthalmic goiter is largely responsible for the increased metabolic demands of that disease. While this may be a factor, it probably is a minor one. Aub, Bright and Uridil[1] studied the effect of thyroxin on the basal metabolism of cats. They found an increase of metabolism following the administration of thyroxin that could not be explained by increased muscular activity, muscular fibrillation or increased muscle tone, and concluded that thyroxin was a direct stimulant of oxidation of the body cells. It is a frequent clinical observation that hyperthyroid patients without any appreciable tremor have an exaggerated basal metabolic rate. Hamburger first called attention to the clinical entity and he has called the condition "masked hyperthyroidism."

From our results it is apparent that chorea, itself, does not greatly alter the basal metabolism. Tests were made both early and late in the disease, and the latter were only slightly lower than the former.

All readings were made before the muscular contractions and twitchings were marked, since it was impossible to get proper readings during the height of the disease. Increased muscular activity undoubtedly raises metabolism, but its study would involve more elaborate apparatus. It is also true that a developed active chorea presents no differential diagnostic problem as it is recognized at sight. However, the early and late phases of chorea when satisfactory basal metabolic rates can be determined by the common types of machines in clinical use are conditions that might simulate mild hyperthyroidism.

Conclusions. 1. The basal metabolic rate was measured in 42 children suffering from acute Sydenham chorea and found to be within normal limits.

2. The severity of the chorea apparently did not affect the metabolic rate.

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CHRONIC CIRCULATORY EFFECTS OF TOBACCO AND NICOTINE.

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For a generation or more, there has been accumulating a mass of laboratory and clinical data which has been interpreted as indicat-

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ing a causal relation between the use of tobacco and organic circulatory disease. A careful analysis of the literature revealed that most of the work was improperly controlled and the reasoning highly uncritical. Confirmation or denial was therefore indicated. In connection with another study, material became available for the present investigation, which we believe definitely refutes the many teachings of the past, especially as to the rôle of nicotine in the production of lesions of the heart and blood-vessels.

In 1902, Esser[20] described degenerative changes in the vagus nerves of dogs chronically poisoned with nicotine salts. He failed to find degenerative changes in the heart muscle, and concluded that the cardiac irregularities in heavy smokers reported by earlier writers, were due to the degenerative changes in the cardiac nerves. Several papers appeared in the years 1906 to 1908[1,4,7,22,23,40,42a,78] reporting changes in the media of the aorta of rabbits given doses of nicotine, tobacco infusion or solution of tobacco smoke. Some of the experimenters administered the poison by stomach tube, others by intravenous or subcutaneous injections. In most instances; there was no mention of the number of animals employed, and only one experimenter[42a] in this period reported the examination of the blood-vessels of control animals. Lesieur[42a] controlled his experiments by administering infusion of denicotinized tobacco to one group of rabbits and infusion of ordinary tobacco to the other group. None of the rabbits which received the denicotinized tobacco showed vascular degenerative changes. Little weight can be given to this report since "denicotinized" tobaccos contain one-fourth to one-half as much nicotine as untreated tobaccos, a fact not appreciated at the time of Lesieur's experiments. All of these early writers mentioned degenerative changes in the media. Some described aneurysms of the aorta[1,7,22] athermatous plaques[4,7,22] and changes in the intima.[22] Adler and Hensel[1] denied degeneration of the intima, or inflammatory lesions; the pathology of the media they characterized as degenerative or calcareous, similar to that produced by epinephrine. There were, however, no cerebral hemorrhages, in contrast to epinephrine.

Some years passed before general interest was again aroused in the vascular effects of chronic tobacco poisoning. Clinical opinion was divided as to an elevation of blood pressure in chronic smokers. Studies by Brigham,[8] Earp[18] and W. M. Johnson[33] showed no difference in blood pressure between smokers and non-smokers, but W. F. Dixon, the pharmacologist[17] affirmed that chronic smokers exhibit a hypertension, and Knopf[34] accepted the dogma that smoking augments cardiovascular disease. Külbs[35] described 3 cases of hemiplegia which he attributed to tobacco.

Pawinski[51] reported that 42% of cases of coronary disease were in heavy smokers, but that only 23% of generalized arteriosclerosis were from this group. Ralli and Oppenheimer,[54] Cornwall[13] and Moschcowitz[47] accepted the view that some cases of angina pectoris

are due to tobacco smoking, and Plenge[53] observed coronary sclerosis, due chiefly to connective tissue replacement of the muscle and elastic fibers of the media, with evidence of fresh necrosis also, in two supposed victims of tobacco smoke. As early as 1915, Brooks[9] attempted an experimental study and saw necrosis of the myocardium, especially of the papillary muscles in rabbits injected with nicotine.

The lesions of thromboangiitis obliterans are well recognized and are known to be statistically related to the use of tobacco (Silbert[61]). Proof of a cause and effect relationship is lacking, although several investigators[25,26,68a,b,69] have shown a high incidence of skin sensitivity to tobacco in this disease. Some constituent other than nicotine was responsible for the skin reactions.

During this period of active clinical interest Romm and Kuschnir[55] renewed the experimental attack. They injected some rabbits with epinephrine, others with nicotine. Epinephrine injected rabbits exhibited sclerotic plaques in great vessels and a decreased response of perfused coronary and renal vessels to constrictor and dilator drugs, earlier and more extensively than the nicotine-injected animals. Control animals were studied but the history and treatment of the controls was not described in the article.

Experiences with intravenous injections of nicotine in rabbits were related by Kosbota[35] in 1930; there were vascular lesions similar to those reported by the earlier writers; calcareous plaques were found in the media and the intima was swollen, with fatty degeneration and desquamation of the endothelium. Female rabbits were affected to a greater degree than were males. There were but 4 control animals, out of a total of 21, and no report of observations on the controls was given.

Gangrene of the toes, preceded by blanching of the skin of the toes in male rats chronically poisoned by tobacco extract has been recently reported. The authors, Friedländer, Silbert and Laskey,[21] observed gangrene in toes of but 1 of 12 rats injected with corresponding doses of pure nicotine. Female rats failed to exhibit gangreneous changes, and no such lesions were noted in control rats. Again, it is not clear what treatment the control rats had received.

Numerous other experimental and clinical contributions could be quoted, but it is sufficient to list these among the references.[3,12,28–30,48,49,52,57,58,66,76]

In view of the almost universal failure of the experimenters to adequately control their observations, whereby the effects of diet, weather, infection, handling, and so forth, could be ruled out, we planned the experiments described below. Both rats and rabbits were used.

Method. 1. *Growing Rats.* Growing rats were started on the experiment between the 10th and 60th day of life. There were 6 litters, each of which was divided equally into control and test animals. Except for 3 control females and 3 nicotine-injected females, all the growing rats were

males. There were 34 in all. Injections of nicotine, dissolved in 0.9% saline and neutralized to litmus with dilute hydrochloric acid, were made subcutaneously, twice daily, 6 days per week and once on Sunday. The dilution was at first 1 part nicotine in 10,000 parts of saline. This concentration was increased finally to 1 to 1000 or 1 to 500 as the animals grew larger, so that while the initial dose for very young rats was but 0.05 cc., the final dose was 0.3 cc. to 0.5 cc.. In all cases the morning dose was adjusted to produce mild convulsions. The evening dose was always the same as the morning dose, but as was mentioned in a previous report[72] the symptoms following the second injection of the day were milder than in the morning. *Litter mate controls received twice daily injections of saline*, the volume of fluid corresponding to that administered to the test animals. Each cage contained both control and test rats, in order that all uncontrolled factors might be the same for all rats. The duration of the experiments on the growing rats was from 3 to 6 months.

2. *Adult Rats.* For adult rats, we were unable to obtain litter mates throughout, but half-sisters or closely related rats from a uniform stock of females were available. Because of an interest in certain other possible effects of nicotine only female rats were included in the adult group. Of these, there were 20 rats, equally divided between control and test groups.

3. *Rabbits.* Each of 2 litters of rabbits was divided equally into control and test groups, which were treated in a manner similar to the rats. In the control group were 3 males and 3 females; in the test group, 4 males and 3 females. The first injection was made at the age of 29 days and the last at the age of 115 days, except for 1 control male which was lost by accident on the 20th day of the experiment.

Rats and rabbits were killed with chloroform on the day after the last injection. The thoracic contents, with the aorta down to the iliac bifurcation, the liver and kidneys were taken out *en masse*. The right and left chambers of the heart were exposed and the aorta opened from heart to bifurcation for gross study. The skin was removed from hind limbs, which were preserved in 4% formaldehyde with the other tissues. Pieces of tissue were then cut for paraffine imbedding or for frozen section. The portions of tissue taken for sectioning were the left circumflex coronary artery with adjacent heart muscle, the arch of the aorta, the thoracic aorta, the abdominal aorta at the level of the renal arteries, and the popliteal artery. Blocks were cut out of the kidney and liver, also.

The paraffine blocks were sectioned at three levels and stained with hematoxylin and eosin or with Mallory's elastic tissue stain. Frozen sections of the tissues of the adult rats were stained with Sudan III to demonstrate any fatty degeneration which may have occurred.

All the above experiments and procedures were carried out in the Department of Pharmacology and the tissue sections were examined by both authors.

Results. Two control rabbits, 2 nicotine-injected rabbits and 1 control rat exhibited Mönckeberg's type of sclerosis of the media of the aorta; 1 control rat suffered from slight degeneration of the media of the popliteal artery and 1 control rabbit developed slight thickening of the coronary artery. No other lesion of the circulatory system was noted. However, during the course of another experiment, some observations were made which have an important bearing on the interpretation of the results of Friedländer, Silbert and Laskey.[21] They were as follows:

Chronic Nicotinism in Paired Rats. Of 25 pairs of adult rats, a test pair was separated from a control pair by a hardware cloth

partition in each of 25 cages. Treatment was in all regards the same as in previous experiments. In view of the report of Friedländer, Silbert and Laskey, the feet of these rats were carefully watched for the development of gangrenous degeneration. Contrary to the findings of these authors, we found such degeneration occasionally in both male and female animals, and in both control and test animals. *Furthermore, in a large cage of 12 stock male rats, closely related to the experimental rats, 8 animals developed marked gangrene of the toes.*

Comment. The fact that clear cut degenerative changes occurred in our control groups as well as in the test animals, indicates how little weight can be given to the uncontrolled experiments of the early part of this century. This is especially so since the number of animals in these early investigations was either very small (only 2 in Lee's study) or not given. One cannot so easily dismiss the experimental findings of Romm and Kuschnir[55] and of Friedländer, Silbert and Laskey.[21] It is clear that their observations were better controlled than those of earlier experimenters; but in view of the appearance of gross lesions of the toes of our control rats, their conclusions must be viewed with considerable doubt. Such observations as those of Plenge[53] on human cases must be viewed with skepticism because of the lack of adequate control.

The recent inquiries into the rôle of sensitivity to tobacco in vascular disease requires serious consideration. Harkavy[25,26] and Sulzberger[68a,b,69,70] independently examined patients with angina pectoris or thromboangiitis obliterans for skin sensitivity to tobacco and to nicotine. Whereas 76% of such cases exhibited positive patch tests with tobacco, only 36% of smokers with Buerger's disease and 16% of non-smokers gave positive reactions. Nicotine was shown not to be the ingredient responsible for the positive skin responses. Neither Harkavy nor Sulzberger believed they had proven a relationship between tobacco and vascular disease, but considered their data to be suggestive. In this we concur.

The early writers believed that the lesions they saw in experimental animals were due to the repeated vasoconstriction following daily administrations of nicotine or tobacco. Tests of human blood pressure effects during and following smoking have not given uniform results. Most of Lee's subjects[40] suffered a blood pressure rise, which was less in "tolerant" smokers than in novices. Coller[44] found a rise of blood pressure when his subjects smoked tobacco, but fake smoking produced no pressor effect. Aikmann[2] and Thompson and Sheldon[73] reported that as many, or more, subjects exhibited a fall of blood pressure as responded to smoking with increased vascular tension.

Very little attention has been given to the possible deleterious effects of acute tobacco vasoconstriction in the presence of actual vascular lesions of other etiology. That there is vasoconstriction during and for an hour after smoking has been accepted for a long

time and that the vasoconstriction is due to nicotine was demonstrated by Lesieur.[42b] Hoskins and Ranson[31] pointed out that the vasoconstrictor effects of nicotine are due to a central as well as sympathetic ganglion stimulation. Stimulation of the adrenal medulla, with increased secretion of epinephrine, has been added as a hypertensive factor in animals.[11,15] Stewart and Rogoff[65] could demonstrate no effect of nicotine on epinephrine secretion, and criticized Cannon, Aub and Binger[11] and others for using uncritical methods. More recent experiments[19,37,41,56,60,67,71] however, lend strong support to the probable stimulation of the adrenal medulla by nicotine.

That smoking actually produces vasoconstriction and slowing of capillary circulation of the extremities in the human has been amply demonstrated by studies of organ volume[10,62] skin temperature [32,44,45,77] and blood flow[38] before, during and after smoking. The vessels of the forehead and abdomen were not affected. Assuming an existing vascular disorder, such as thromboangiitis obliterans or diabetic sclerosis (Blotner[5]) with the tissues on the verge of gangrene, it is logical to suppose that a vasoconstriction due to tobacco may further decrease the nutrition of the tissue to the point where gangrene would result.

Experiments on the coronary vessels do not so readily support a relationship between angina pectoris and tobacco. Reports from two separate laboratories in 1933 described increased coronary flow. Laubry, Deglaude and Walser[39] measured the coronary flow in isolated rabbit heart, and found an increased coronary circulation with infusion of tobacco and with nicotine in all but excessive doses. Mansfeld and Hecht[46] introduced tobacco smoke into the lungs of the heart-lung preparation of dogs and found only coronary dilatation and increased cardiac output. Bond and Hirschfelder had a similar experience many years before. Although the irregularities of cardiac rhythm occurring in certain patients addicted to heavy smoking have been reproduced in animals,[20,64] these irregularities scarcely contribute to an explanation of angina pectoris. A possibility which occurs to the writers is that there is sufficient increase in epinephrine output to accentuate the symptoms of this malady. That epinephrine does precipitate an anginal attack is accepted by clinicians[14] but that smoking increases the epinephrine output in man is only indirectly suggested by none-too-well confirmed reports of increased blood sugar following smoking.[6,16,24,43] Animal experiments usually show an increase of blood sugar[27,41,50,63] and some of them indirectly indicate an adrenal factor[41] but the doses used were larger than would be obtained through smoking of tobacco. Boldyreff[6] attributed the hyperglycemia to some other factor than nicotine.

White[75] observed transient electrocardiographic changes resembling those of coronary obstruction in a man who exhibited anginoid attacks on smoking, but he considered the change purely

functional. Perhaps the clinical measurements of respiratory function by Turley and Harrison[74] and of circulatory response to work[49] with figures slightly, but perhaps insignificantly, in favor of abstainers from tobacco, have some bearing on the subject. However, we must not overlook conclusions of Sharber and White[59] from clinical data that there is no statistical relationship between tobacco and angina pectoris, in view of the fact that there was as high an incidence of angina among non-smokers as among smokers.

Since we have no data relating to the subject, we do not care at this time to discuss "tobacco amblyopia," which recent clinical experience suggests is due to constriction of the vessels supplying the retina.

Summary. 1. Experimental and clinical studies supporting the thesis that chronic tobacco or nicotine poisoning leads to degeneration of circulatory organs, are poorly controlled and therefore of doubtful value.

2. Experiments of the present authors show greater vascular degeneration in control animals than in animals chronically poisoned with nicotine.

3. It is suggested that acute peripheral vasoconstriction associated with smoking may exaggerate the effect of existing vascular disease upon the nutrition of the extremities.

4. Smoking probably does not produce organic disease of the heart.

Since the proof was returned to the editor's office, two papers have come to our attention. Harkavy (*Proc. Soc. Exp. Biol. and Med.*, **36**, 381, 1937) reported confirmation of the results of Friedländer, Silbert and Laskey with "nicotine-free" extracts of tobacco, and furthermore showed sensitization of segments of intestine of injected rats to the extract. This important contribution further removes nicotine from its alleged rôle as an etiologic agent in vascular degeneration, and emphasizes the insecure ground of prescribing "nicotine-free" tobacco for patients suffering from Buerger's Disease.

Staemmler (*Virch. Arch. f. Path. Anat.*, **295**, 366, 1935) found no vascular lesions in rats chronically poisoned with nicotine, although adrenals and testes were markedly affected.

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THE LUCID INTERVAL AND ACUTE APPENDICITIS.

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A review of the results of the management of patients suffering with acute appendicitis complicated by spreading peritonitis on our services in 3 hospitals, over a period of 4 years, shows that in every instance where death occurred the surgeon did not diagnose the condition pre-operatively. The most frequent error made by both ward and attending surgeon was the failure to recognize the early

perforative appendix with beginning spreading peritonitis; in 85% of instances a diagnosis of acute appendicitis only was made. The second most frequent error was their inability to diagnose the gangrenous appendix in the pre-perforative state.

In this discussion the latter group only will be considered. Examination of the clinical records showed that invariably the patient gave a typical history of appendiceal colic before admission, the attending physician elicited localized tenderness in the right lower quadrant and diagnosed appendicitis. Directly before admission, however, all symptoms and signs had disappeared, except a moderate or slight elevation of temperature. Increased tension, rigidity, free fluid and distention were absent. There was, however, diminution of peristalsis. Without exception, the lesion responsible for this "lucid interval" was partial or complete gangrene of the appendix.

In surgery, the word "lucid" has been used to describe a period of mental clearness which occurs between an initial semiconscious or unconscious state and coma in patients who have experienced cranial trauma; this is most frequently observed in rupture of one of the branches of the middle meningeal artery with a resultant extradural hemorrhage. During the lucid interval, the patient may converse normally and present no signs of intracranial change. The duration of this period is dependent upon the rapidity with which the blood escapes from the ruptured blood-vessel and the reaction of the compensatory mechanism to the increased intracranial pressure.

The "lucid interval" as we use it in connection with gangrenous appendicitis is the symptom sign-free period preceding perforation and is dependent upon factors which influence intra-appendiceal pressure. The subsidence of pain, remission of temperature, the absence of tenderness, increased tension or rigidity are due in part to a reduction of intra-appendiceal pressure. The symptoms and signs accompanying an acutely inflamed appendix prior to the development of gangrene are associated with and partially dependent upon increased intra-appendiceal pressure.

At the onset there is usually an obstruction of the lumen of the appendix, due either to a fecolith or a mucopurulent plug. Venous congestion followed by the mobilization of neutrophils, with a consequent swelling of the mucosa and submucosa, local necrosis and formation of gas and pus, all tend to increase intra-appendiceal pressure; the absorption of these products of inflammation tends to diminish it; this varying pressure in all probability accounts for the intermittent pain in the early stages of the disease. During this active period the serosa of the appendix withstands tremendous pressure, because of which death of the tissues beneath is hastened. However, when the pressure becomes so great that the cells of the serosa itself become devitalized, it expands. In gangrenous unruptured appendices we have observed on careful inspection a separation

of the serosa from the tissues beneath. Frequently pus can be seen in yellowish streaks beneath the intact peritoneal coat, on the surface of the devitalized muscularis. Following the death of the serosa, the "lucid interval" is fully established.

Pain is absent because the nerve terminals have become devitalized. Without careful study, this lucid period of gangrene cannot be differentiated from the period accompanying recovery. The reason for this is apparent: inflamed tissues are overdistended tissues and a return toward normal is associated with a diminution in size and a reduction in pressure brought about mainly through absorption by way of the lymph or blood streams. A small amount of gas or infectious material may escape from the lumen of the distal portion into that of the proximal portion of the inflamed appendix or into the cecum. This slight reduction in pressure lessens venous congestion, the capillary circulation improves, absorption of the products of bacterial activity by the lymph and blood streams is increased and resolution follows.

The frequency with which the symptoms and signs associated with gangrenous lesions of the appendix resemble those of resolution is dependent, 1, upon the management of the patient; 2, the extent of gangrene; and 3, the situation of the appendix. Frequently a physician makes a diagnosis of acute appendicitis, withholds laxatives and fluids by mouth and sends the patient into the hospital. The lucid interval, however, may occur during the time that lapses between the diagnosis and admission to the hospital and accounts for the frequent statement of the patient to the hospital intern that "it is just like going to the dentist with an aching tooth—the pain has gone."

If the surgeon accepts the diagnosis and operates immediately, regardless of the absence of symptoms and signs, a catastrophe may be prevented. If he questions the diagnosis and fluids are withheld until the gangrenous appendix is quarantined, then nourishment given gradually, an appendiceal abscess usually forms. Under such management the symptoms are generally of mild degree and tenderness may be the only physical sign. Peristaltic sounds are usually absent in the right lower quadrant but present in moderate degree throughout the other quadrants. If, however, he does not accept the diagnosis and allows the patient to take nourishment by mouth, the perforation which follows may be sudden and terrific in its effect. Violent abdominal pain at the site of perforation will occur, accompanied by nausea, vomiting and rise in temperature associated with general abdominal rigidity, absence of peristalsis and the presence of free fluid.

The normal appendix has peristaltic waves, but there is no method that we have discovered to determine their presence clinically; neither can we show the effect that inflammation has on the contraction of the muscular coats. In the dog, peristaltic waves occur in the

normal appendix and laxatives stimulate them; we do not know definitely what happens after the onset of acute inflammation. We were unable to produce peristalsis or perforation of a completely gangrenous appendix by inducing violent peristalsis of both ileum and cecum with the use of laxatives. At least, it did not occur under direct observation, despite the use of Epsom salts, castor oil and hypodermic injections of eserine. The last produced violent peristalsis in both large and small intestines within 4 minutes of the injection.

While the management of the patient before he is admitted to the hospital is the greatest factor in influencing the frequency with which the lucid interval is confused with a regressing inflammation of the appendix, the extent of the involvement of the appendix in the gangrenous process is also very important. Complete gangrene involving all of the coats resulting in a uniformly black appendix is not commonly observed at operation. The usual type is one in which the mucous and muscularis are only partially involved. The size, number and position of fecal concretions in the lumen of the appendix influence the degree of devitalization. There are cases, however, in which embolic factors play a very important part: according to some investigators this occurs most frequently in the later decades of life. It has been our experience that the greater the amount of tissue involved in the gangrenous process, the more complete the period of lucidity.

An abnormally situated appendix makes the differentiation between resolution and early gangrene even more difficult, particularly if the appendix has been previously inflamed. The initial general colicky pain may not even occur, the attack starting with localized pain. Because of the development of a local tissue immunity, the temperature reaction may be slight or normal and abdominal tenderness absent if the appendix is retrocecal or low in the pelvis. Regardless of the location, however, perforation of a gangrenous appendix into the general peritoneal cavity is delayed not only by changes which occur beneath the serous coat but in the peritoneal cavity as a whole and in the tissues contiguous to the diseased organ. These changes are brought about by the absorption of toxin acting on the hematopoietic system and on the plexuses of nerves, within the abdomen: the mobilization of the neutrophils followed by the larger phagocytes (clasmatocytes), is an example of the former; and the hyperemia of the peritoneum followed by a general outpouring of serous exudate, a local formation of fibrin and a diminution of peristalsis is an example of the latter.

The toxins that are absorbed through a gangrenous appendix are easily taken care of by this defensive mechanism, as evidenced by the absolutely safe procedure of closing the peritoneal cavity without drainage, following the removal of a non-perforated gangrenous appendix. When the serous coat is broken, additional defensive measures are necessary. Antibodies are formed to combat toxins

in the blood stream. The large central organs, chiefly the spleen and liver, are called into action. Prognosis is dependent, to a great extent, not on what Nature does, but rather on how the patient is managed. The decisions of those in charge influence the outcome.

If the natural body defense is supported by a management which does not interfere with the protective measures already instituted, local tissue as well as general immunity develops and the patient recovers. If the development of one or the other or both is interfered with, the patient will frequently succumb.

The gross changes which occur in the development of a local tissue immunity are characteristic. In man, if the process is limited to the appendix, hyperemia is followed by a decrease in the vascularity of the peritoneum which appears gray and edematous and is frequently covered with a protective layer of fibrin. The omentum, which is often adherent to the appendix or cecum, is thicker, edematous and the venules appear to be dilated. This phenomenon is the result of the reaction of the circulatory, lymph and autonomic nervous system to bacterial antigens. It is similar to the reaction which occurs in a surface cellulitis, except that in the early stages of peritonitis a uniform erythema is observed, while redness in radiating lines usually definitely marks the lymphatic vessels in a spreading cellulitis.

The diagnosis of the pre-perforative stage—the lucid interval—of acute appendicitis is dependent upon the following: 1, A complete history; 2, a thorough physical examination; 3, noting on the patient's clinical record the physical findings of the physician who first examined him; 4, a careful differential count, with observation on the ratio of mature and immature neutrophils and also the relative number of degenerated immature forms.

1. *A Complete History.* Three important points are frequently missing in the clinical record of the patient operated upon for acute appendicitis in the average hospital: 1, The exact time the pain began; 2, whether or not a laxative was administered, the time of administration, the character, kind and size of the dose or doses; and 3, when and how much opiate or sedative was given before admission. Colicky abdominal pain, general at first, the exacerbations centering around the umbilicus, and later localizing in the right lower quadrant, is still the most reliable symptom of an acute inflammation of the appendix.

Other acute lesions of the abdomen requiring immediate surgery, with the possible exception of acute intestinal obstruction, are not accompanied by pain of this character and the lucid interval does not usually occur. In the early stages of acute intestinal obstruction the absence of temperature and leukocytosis, increase in peristalsis, varying degrees of tenderness and a change in the character of the vomitus usually make the diagnosis certain. A lucid interval, however, may accompany acute intestinal obstruction. The early pain associated with this condition is frequently colicky

but may subside when the intestine becomes gangrenous. This lucid interval may be prolonged by withholding fluids by mouth or by the use of the Levin or duodenal tube, the decompression produced by the latter accounting for the improvement in symptoms and signs and perhaps delay in operation. The continuity of the devitalized intestine may last as long as 7 days and when perforation does occur, the pain is not so severe and the physical signs are not so marked as in the usual perforation of an abdominal viscus.

In gangrenous appendicitis the percentage of perforations with the development of a spreading peritonitis increases with the dose and varies with the time of administration of laxatives. Frank perforation with accentuation of pain which is continuous and definitely located by the patient occurs more frequently with than without laxatives and still more frequently with multiple than with single laxatives. The lucid interval is more likely to be overlooked when laxatives have not been given or have been vomited immediately after administration. The likelihood of the latter occurring is less in appendicitis than with acute lesions of viscera in the upper abdomen. Following an acute perforation of the duodenum the patient will invariably vomit the laxative or anodyne, given by mouth, immediately; provided, of course, it is given soon after the onset of pain. Vomiting occurs when the autonomic nervous system attempts to prevent leakage into the peritoneal cavity. In intestinal obstruction the relation of vomiting to laxative administration is dependent upon the site of the obstruction.

There are physicians who persist in giving morphine to patients suffering with acute abdominal pain before making their diagnosis. The resident's problem of determining the character and amount of opiate given to the patient before admission to the hospital is simplified if the attending physician witnesses the operation; if he does not and the patient states that he has received a hypodermic or has obtained relief after taking a pill or medicine, an effort should be made to contact the family physician before operation; this may seem an unnecessary procedure but it is definitely indicated if the patient does not have pain and physical signs are indefinite.

Elevation of temperature is of questionable value as a diagnostic aid because it may be absent in the presence of marked lesions and its remission may mean either gangrene or resolution. In 1927, Bower and Clark[1] reviewed the clinical histories of 750 patients who were operated upon for acute appendicitis and correlated symptoms and signs with the pathologic findings. In 279 patients, there was less than 1° rise in temperature on admission.

2. *A Thorough Physical Examination.* Tenderness is the most important physical sign in acute appendicitis. Its significance, I am sure, is not sufficiently appreciated by the average physician. Tenderness alone in the lower right abdomen, without pain, without nausea or vomiting, fever or leukocytosis, is sufficient at times to make a diagnosis of acute appendicitis.

The technique of the examination for this valuable sign is important. The bed should be so situated that the examiner can walk around it. The patient should be lying in the supine position, no pillow supporting his head, entirely uncovered except for a towel over the pubes. He is told to assume a position which is most comfortable and notation is made if there is any difference in the position of the lower extremities; if the right thigh is slightly flexed, the patient is asked to extend it and is then questioned regarding the relative degree of comfort in each position. A small pillow is then placed beneath the head and neck to relieve the strain on the accessory muscles of respiration. The arms should be placed at the sides.

Standing at the patient's left side, the examiner places his left hand on the abdomen; if the weather is cold the hand should be immersed in warm water before palpation is begun. It is important that the hand be carefully applied to the abdomen; first, the entire hand should be gently laid on the upper left abdomen, not on the right lower quadrant. It should remain there until the examiner feels that he has the patient's confidence. This can only be determined by experience, but a return of normal respiratory rhythm and the patient's permitting the abdominal wall to remain in contact with the hand is evidence that one can proceed. The fingers are then alternately flexed and extended as the hand is moved horizontally along the costal margin; in the same fashion the lower left abdomen is palpated. Following this the upper right abdomen is examined, just as gently and deliberately and finally the right lower quadrant.

From the time the hand is placed on the upper left abdomen until the examination of the right lower quadrant is finished, nothing should be said to the patient. The examiner, however, watches the facial expression, noting any change that may occur. In all quadrants the touch should be light, sufficient only to press the muscles and the parietal peritoneum lightly against the abdominal contents. Following the removal of his hand, the examiner asks the patient to designate the most tender area. If he states that tenderness is absent or that there is no difference in the degree at any point, the knees should then be flexed on the abdomen by placing a pillow beneath the thighs and the hand is applied again to the upper left quadrant and the examination repeated.

Again the patient is asked where the pressure annoys him most and if he indicates the right abdomen an attempt should be made to localize the tenderness more definitely by proceeding this time from the upper right abdomen. If the tenderness is more marked in the lower right quadrant, the procedure advocated by Murphy (tenderness elicited by percussion) is carried out. I have advocated this method ever since I first saw this remarkable teacher demonstrate it at one of his clinics. The second finger of the left hand is flexed to a right angle at the mid-carpal joint, the tip placed on the abdo-

men and the joint struck with the second finger of the right hand. The blow struck by the percussing finger at first must be light—just enough to determine the maximum point of tenderness. It is hardly necessary to mention that the finger tips alone are most sensitive to changes in muscular tension and that palpation of the abdomen should precede percussion tenderness.

I have found the latter valuable in helping to determine the site for the incision in those cases in which the appendix is in contact with the parietal peritoneum. In eliciting tenderness in a patient whose appendix is abnormally situated, the right and left lateral prone positions are sometimes helpful; having the thighs more acutely flexed than in the supine position reduces the degree of tension and organs deeply situated can be more definitely located. Undoubtedly rectal examination is by far the most important aid in differentiating lower from upper abdominal lesions and in helping definitely to diagnose organic disease in a patient who has a hypersensitive nervous system. Contractions of abdominal muscles due to voluntary spasm can be ruled out by this examination. In women, a vaginal examination should be made if possible.

3. *Noting on the Patient's Clinical Record the Physical Findings of the Physician Who First Examined Him.* The physician who first examines a patient with acute abdominal pain has the best opportunity to make a correct diagnosis. This is true, not only during the early but also the successive phases of inflammatory processes involving any of the abdominal viscera, up to the time the terminal stages of a spreading peritonitis develop, when it becomes difficult definitely to determine the organ primarily affected. Fortunately, advanced spreading peritonitis is seldom observed by a physician at his initial visit. The usual history is that more than one visit has been made by the attending physician before the patient is admitted to the hospital.

In the average case this is as it should be. A correct diagnosis cannot always be made at the first examination, but if appendicitis is suspected, and in the presence of acute abdominal pain it must be, the second visit should not be delayed 24 hours: it should not be delayed more than 4. If the physician has made notations of his initial examination, he will observe changes, if not at the end of 4 hours, then surely at the end of 8, which will indicate definitely whether or not the case is an operative one. Unfortunately, the average physician does not make careful notes, which means that the very slight changes significant of advancing or regressing lesions are overlooked.

If then, at the end of 8 hours he is still uncertain, he should ask himself this question: "Is there anything I can do that will help me determine exactly what is wrong with this patient?" What would the physician do if his patient were in a hospital? He would call a surgeon and have a leukocyte count and Schilling hemogram

made immediately. All of these things can be done in the home as well as in the hospital. This is not a plea for more consultation work for the surgeon but a procedure suggested to prevent procrastination, to make possible a closer correlation of history, physical findings and gross findings at operation and to avoid the necessity of explaining why patients are sometimes held at the hospital before they are operated upon.

In defense of the family physician it must be admitted that in many instances, either because of the influence of relatives or friends, patients refuse to accept his advice. To protect himself and emphasize the seriousness of the situation a consultation with a surgeon should be advised and, if the patient refuses, the physician should dismiss himself. Every physician no doubt has had the experience of permitting the wishes of a patient to interfere with what he thinks should be done.

If we could always pre-determine the course disease will take; if in acute appendicitis one could definitely state the number, kind and virulence of the microörganisms at work; if the susceptibility of the patient to these microörganisms were known, one could vary the management accordingly. This being impossible, we must manage the mild, average and severe types in the same manner at the onset. If patients object to operation, they should be told that if the appendix is removed when it is intact, they take only 1 chance in 275 of not withstanding the disease; but if they wait until it ruptures, they take 1 chance in 8, increasing the risk 35 times. These figures are only approximate, but they indicate to patients with ordinary intelligence the risk they assume if they delay.

The surgeon may feel that the onus of the high mortality rate of acute appendicitis is for the most part due to things that happen to the patient before he enters the hospital. The family physician may, and in some instances rightly, criticize various methods of hospital management; but the fact remains that both are at fault in one particular, and that is careful notes pertaining to the physical examination of the patient are not made by either. The surgeon himself seldom writes his findings on the clinical record and no effort whatever is made to obtain those of the family physician. In the average case these notations are not important, especially if the appendix is not ruptured, but in this discussion we are dealing with the unusual case: the one patient in 25. This patient is admitted to the surgical ward as the usual case of acute appendicitis. The resident obtains a history which is typical, but the physical examination discloses no definite information. The chief of the service is duly called. He may see the patient, but more frequently he sends his associate, who in turn is uncertain of the diagnosis. It is at this point that the family physician should be consulted and his physical findings noted on the chart. These findings must be considered if an accurate diagnosis is to be made.

Most patients will consent to operation, but there are a few who doubt its necessity and are anxious to avoid it. These reluctant patients will usually give an accurate history but will not admit that abdominal tenderness is present on palpation. It is wise to talk to the family physician in such cases or, still better, to have him come to the hospital. He and the surgeon both will profit by such a conference. If the physician cannot come, perhaps a member of the family who was present when the examination was made can supply the necessary information. We have been very successful in having the family physician present at operation. Some patients, however, are admitted direct from the dispensary without having previously consulted a physician. In such cases, the notes of the physician in the receiving ward are available.

4. *Careful Differential Count With Observation on the Ratio of Mature and Immature Neutrophils and Also the Relative Number of Degenerated Immature Forms.* A neutrophil leukocytosis in a patient suspected of having an acute appendicitis is of diagnostic value in at least 80% of cases. A Schilling hemogram, if made by a competent clinical pathologist, is of additional value. The report of a resident physician, recently assigned to laboratory duty, on the ratio of mature and immature neutrophils and the relative number of degenerated immature forms cannot be relied upon. The greatest value of the Schilling lies in a comparative study of repeated hemograms made by a clinical pathologist who is intimately acquainted with the clinical aspect of the case. Just as the surgeon visits the Roentgen ray laboratory and confers with the radiologist regarding his deductions on the lesion present in a given case, so should he confer with clinical pathologists in cases of doubtful diagnosis of inflammatory origin.

Conclusions. The high mortality of spreading peritonitis complicating acute perforative appendicitis (27 to 40% in the United States) is in part due to the failure of physicians and surgeons accurately to diagnose the acute lesions of the appendix in both preperforative and early postperforative states.

Partial or complete gangrene of the appendix is frequently associated with a subsidence of symptoms and absence of physical signs—the so-called "lucid interval." This is confused with the resolution following an acute involvement of the appendix of less virulent character. The subsidence of symptoms and signs accompanying both is due to diminished intra-appendiceal pressure: the relaxation incident to devitalization of the serosa in the first instance, the absorption of the products of inflammation in the latter. In this communication we have endeavored to emphasize pertinent points which may aid in the recognition of this "lucid interval."

REFERENCE.

(1.) **Bower, J. O.**, and **Clark, J. H.**: J. Am. Med. Assn., **89**, 844, 1927.

BOOK REVIEWS AND NOTICES.

PHENOMENON OF LOCAL TISSUE REACTIVITY AND ITS IMMUNOLOGICAL, PATHOLOGICAL AND CLINICAL SIGNIFICANCE. By GREGORY SHWARTZMAN, M.D., Bacteriologist, Mount Sinai Hospital, New York. Foreword by JULES BORDET, M.D., Paris. Pp. 461; 47 illustrations and 1 colored plate. New York: Paul B. Hoeber, Inc., 1937. Price, $7.50.

IN 1927 the author observed for the first time a peculiar reaction in the skin of rabbits. When he injected a filtrate of typhoid bacilli intradermally only minimal inflammation followed. But if 24 hours later he gave a second injection, this time intravenously, a violent inflammatory reaction occurred at the site of the skin injection, with hemorrhage and necrosis. This is the famed Shwartzman phenomenon. In some way that is even yet not understood, the skin injection alters the tissue locally in such a way that it reacts to an irritant in the blood stream. Certain other bacteria may be substituted for the typhoid bacilli. Moreover, the reaction is not a specific one, for the cutaneous injection may be made with the filtrate of one organism, the intravenous injection with the filtrate of another.

The present monograph summarizes the work of the author and that of many others who have worked on the phenomenon, up to the beginning of 1936. Among the subjects discussed are the nature of the substance that prepares the skin for the reaction—the subject is antigenic and is of the nature of bacterial soluble toxin; the regression brought about in mouse tumors by intravenous injection of the bacterial filtrate; the distinction between the Shwartzman phenomenon and anaphylaxis as well as the Arthus phenomenon; the probable relation of the phenomenon to human hemorrhagic diatheses and hemorrhagic infections; and the therapeutic effect of serums prepared against bacterial filtrates, in the treatment of human typhoid fever, meningococcic meningitis and ulcerative colitis.

The photomicrographs are numerous and excellent. M. McC.

RECENT ADVANCES IN INDUSTRIAL HYGIENE AND MEDICINE. By T. M. LING, M.A., B.M. (OXON.), M.R.C.P. (LOND.), Senior Medical Officer, Bristol Police, etc. Foreword by J. A. NIXON, C.M.G., M.D., F.R.C.P., Emeritus Professor of Medicine, University of Bristol, etc. Pp. 212; 29 illustrations. Philadelphia: P. Blakiston's Son & Co., Inc., 1937. Price, $3.50.

IN this book the author has endeavored to bring together a number of the modern advances which have been made in industrial hygiene, though of 167 citations over half are from before 1930. On the whole, the work is well done considering the small size of the volume, though one regrets the omission of various subjects of live interest. Little if any space is given to biologic agents as industrial hazards, such as those causing tuberculosis, syphilis, anthrax and epidermophytoses. Too little space is given to metallic poisons (lead only being discussed) and to volatile solvents (benzol and its homologues and trichlorethylene only being considered). No space at all is given to changes of atmospheric pressure, such as those causing compressed air illness.

The bibliography following each chapter is quite helpful, though it is to be regretted that there are not more references to American work. Very few German references are cited, and only one or two French, though

much good work has been done on the Continent. Unfortunately 43 citations are given for which no references appear.

Considering in more detail the subject discussed, the chapter on Medical Supervision gives an excellent presentation of the duties of the industrial physician. Industrial accidents and their significance and neuroses and industrial fatigue are well presented in considerable detail. There is also a good, well-organized discussion of industrial lighting.

The chapter on ventilation is somewhat disappointing, but contains some good material. The discussion of local exhaust ventilation is inadequate and the importance of proper hood design is not emphasized. Air conditioning as understood in the United States is not clearly described.

The chapters on dust is well written and comprehensive considering the space allowable. A decrease in silicosis in England, due to the preventive measures taken, is noted. It is wisely emphasized that respirators should not be relied upon wholly to protect workers from excessive dustiness, but rather some influence external to the workman.

The chapter on noise is excellent and well worth reading. Noise is cleverly defined as sound at the wrong time in the wrong place.

Lead poisoning, which still heads the list of notifiable diseases in England, is very well handled. Periodic basophilic red cell counts are stated to be an excellent check on workers and on working conditions, but the author fails to refer to McCord's work thereon. There is one grave error in the discussion of the treatment of severe lead colic. Aub is quoted as advising the hypodermic use of ammonium chloride (15 cc. of a 5% solution), whereas he actually advised the use of calcium chloride, which would have an opposite effect.

The consideration of industrial gases is rather meager. Henderson and Hagard's classification is referred to, but only 1 of the 4 main headings therein, asphyxiants, is given, and one subheading, anesthetic gases, under their Group III. Carbon monoxide, the carbonyls, and hydrogen sulphide are the only gases included, and benzol and its homologues and trichlorethylene (the formula for which is wrongly given) are the only volatile solvents. Lung changes found in welders' and dyeworkers' cancer are included in this chapter.

The rapid increase in both the numbers of volatile solvents used and in uses therefor, and in discussion of their toxicity in recent literature, warrants more extended references to this group.

The growing importance of industrial dermatoses is indicated by the table and graph presented, but the only conditions discussed specifically are bakers' dermatitis and chrome dermatitis. No reference to the value of patch testing in diagnosis appears. H. S.

THE MACHINERY OF THE BODY. By ANTON J. CARLSON and VICTOR JOHNSON, The University of Chicago. Pp. 580; 187 illustrations. Chicago: The University of Chicago Press, 1937. Price, $4.00.

ONE of the most difficult problems in education is to present in simple language the elementary facts of a complicated subject such as physiology without distorting these facts. The authors have solved this problem and have consequently established their reputation as teachers on as high a plane as that they have attained in original research. The subject matter is presented with admirable simplicity and clarity and is illustrated by excellent diagrams. Excellent generalizations are made which enable the student to compare, for instance, inhibition in the heart with that in the nervous system. The functions of the endocrine glands are well described with all the clarity possible with our present knowledge. The history of each subject is sketched in an interesting manner and references are given to some books of general interest. H. B.

SYPHILIS. The Next Great Plague To Go. By MORRIS FISHBEIN, M.D. Pp. 70; illustrated. Philadelphia: David McKay Company, 1937. Price, $1.00.

WITH the campaign that the Surgeon-General of our Public Health Service is now urging against syphilis, small inexpensive handbooks for the laity are useful adjuncts and, incidentally, should have an excellent sale. Such a booklet from the editor of the *Journal of the American Medical Association* should command especial attention and it is hoped that many will get from it some idea of the cause of the disease, how it is spread, its symptoms, and how it is diagnosed, treated and prevented. The very prominence of the author, however, makes it extra necessary that, once embarked on the venture, he take the necessary time from his busy schedule to write an accurate, balanced presentation. We do not feel that this has been the case: In the first 14 of the 70 pages there is "meat" in less than one; saving here would have permitted a much less inadequate statement in vitally important parts, such as the tertiary stages, the cardiovascular system, paresis, tabes dorsalis, prophylaxis and so on. As examples of material that one would wish to see differently presented: The illustration of Hutchinson teeth is far from typical; interstitial keratitis should not be regarded as "the most characteristic signs of syphilis" at birth; the causative organism is pale-staining, not pale; it is not generally accepted that Columbus' sailors brought syphilis to Europe. A practitioner friend complains that the section on treatment is not as clearly set forth as even a booklet of this size should permit, and that it is incorrect to say that those who react badly to drugs constitute the 10% of incurables. At least a few references to guide toward fuller reading would be helpful. Altogether let us hope that it will be a better "handbook for everyone," or a careful revision of this one, that will be in the forefront of the present campaign.

E. K.

APPENDICITIS. A Clinical Study. By W. H. BOWEN, HON. M.A. (CAMB.), M.S. (LOND.), F.R.C.S., Hon. Surgeon to Addenbrooke's Hospital, Cambridge; Hon. Consulting Surgeon to Royston County Hospital; Examiner in Surgery, University of Cambridge, etc. Pp. 202. Cambridge: The University Press, 1937. Price, $2.50.

THIS interesting little monograph is, as the author intended it to be, essentially a clinical study. It aims to give the student and practitioner an outline of the common varieties of disease of the appendix. There are 11 chapters, beginning with etiology, and including diagnosis, treatment and complications. Subacute and chronic appendicitis are discussed. The relationship of purgation to perforation has been stressed. The association of stercoliths with appendiceal obstruction and the part which obstruction plays in the progress of the disease are briefly, but ably, reviewed, and the author states "It is clear that the etiologic factor in the severe grades of appendicitis is the stercolith." Paraumbilical or transverse abdominal pain passing to the right iliac fossa he believes to be the most important single finding in the differential diagnosis. The section on treatment is well written. The various viewpoints in regard to conservative *versus* immediate operative treatment in the late cases are thoroughly covered. The author prefers Battle's incision in acute appendicitis. A very interesting chapter is that dealing with chronic appendicitis. The author states that "provided that there is careful analysis of the past history, signs and symptoms and any collateral investigations which seem necessary, the figures suggest that surgical treatment can prove successful in a high percentage of cases." This little volume will be cordially received, as well it should be.

I. R.

RUSSIAN MEDICINE. (Vol. XX of Clio Medica.) By W. HORSLEY GANTT, M.D., Johns Hopkins University School of Medicine; formerly Chief of Medical Division, American Relief Administration, Leningrad Unit (1922-1923); Collaborator in Pavlov's Laboratories (1925–1929). Pp. 214; 12 illustrations. New York: Paul B. Hoeber, Inc., 1937. Price, $2.50.

THE author divides the history of medicine in Russia into four periods: 1, The primitive period, which extended to the time of Peter the Great; 2, the reign of Peter, during which he founded hospitals and medical schools, and sought to introduce western medicine into his country; 3, the rise of independent Russian medicine in the nineteenth century; 4, state medicine under the Soviet régime.

During the primitive period there was no organized medical education in Russia. The people depended for their medical care on witches and wizards, seers and wolfmen, and all treatment was either based on magic, charms, incantations, prayers, etc., or purely empiric by means of herbs, steam baths, bloodletting, etc. There were no hospitals except a few infirmaries attached to monasteries. Foreign doctors occasionally came to Russia, generally sent by some potentate as an act of courtesy to the tsar; but they remained at Court, and only performed their professional duties to the tsar and his entourage. Peter the Great made strenuous efforts to introduce western medicine in his country. He established medical schools and hospitals and imported teachers. Among other things he purchased the celebrated anatomic museum of Ruysch, and along with it the secret of the Dutchman's method of injecting specimens, and he sent Russian students abroad to study medicine. The enlightened Empress Catherine II did much to elevate the status of Russian medicine, especially when she brought the Englishman, Dimsdale, over to introduce inoculation for smallpox. She also greatly aided the furtherance of medical education by enlarging the scope of the medical schools. During the third period, the nineteenth century Russian medicine made great strides. Great hospitals were established, the medical schools flourished, especially the Military Medical Academy at Petersburg, to which was attached a medical library which Garrison ranked as equal with that of the British Museum and the Surgeon-General's in Washington. Much of this progress must be attributed to some of the really great men whose work won international renown. Sir James Wylie, a Scotchman, who came to Russia as physician to Prince Galitzin in 1790, organized a splendid army medical service and built up the famous Military Medical Academy; Karl Ernst von Baer, the founder of modern embryology; Pirogov, one of the greatest military surgeons of all time; Botkin, the great clinician who did so much for the study of clinical pathology, were worthy predecessors of Mechnikov and Pavlov. The author names many other famous scientists and practitoners who raised Russian medicine during this period to its greatest heights.

The author draws from personal observation a terrible picture of the famine in Russia in 1920–1921, when human flesh was sold in markets and members of families killed their own blood relatives for food. He concludes his work with a valuable and apparently impartial review of the state of Russian medicine under the Soviet government.

This little book presents in concise form an excellent picture of the development of medicine in a great country which has only become civilized in a comparatively few hundred years. It contains a number of excellent illustrations, and a most useful table of comparative chronology. The author is well qualified for his task having served in Russia as a member of the American Relief Administration in 1922–1923, and worked with the lamented Pavlov for five years. He has performed a difficult task in a most able manner. F. P.

RECENT ADVANCES IN THE STUDY OF RHEUMATISM. By FREDERIC JOHN POYNTON, M.D., F.R.C.P. (LOND.), Consulting Physician, University College Hospital and the Hospital for Sick Children, Great Ormand Street; and BERNARD SCHLESINGER, M.A., M.D. (CAMB.), F.R.C.P. (LOND.), Physician to Children's Department, Royal Northern Hospital; Physician to Out-patients, Hospital for Sick Children, Great Ormand Street. Pp. 380; 51 illustrations. Second edition. Philadelphia: P. Blakiston's Son & Co., Inc., 1937. Price, $5.00.

THIS is a review of current trends of thought in the study of rheumatism, including a consideration of etiologic and predisposing factors, pathology and treatment. The authors, who have had extensive clinical and experimental experience, have presented a reasonably coherent and complete picture of arthritis in childhood and chronic arthritis in the adult. Their critical viewpoint recognizes that many more fundamental facts are needed before a completely satisfactory therapeutic regimen can be devised. Yet their attitude toward therapeutic measures is pragmatic, maintaining an open mind toward the utility of measures not yet fully understood.

The book first deals with acute rheumatic disease in children, then with chronic rheumatism. The first portion presents a detailed description of the underlying pathology, though the precise nature of the responsible agents is still a matter of debate. The blood and tissues seldom yield viable microörganisms, and these often form different strains; though the blood serum may show high concentration of antibodies against streptococci, this evidence is not sufficiently specific to implicate any single strain. Furthermore, relapses may occur when the level of circulating antibodies is at its height. It is suggested that the most probable explanation is that streptococcal infection lowers the defense against a virus, because virus bodies are found in pericardial fluids; the lesions are similar to those produced in known virus diseases. The possibility that allergic phenomena are responsible is held to be plausible only. The use of various drugs is described, although the full mode of their action is unknown.

The second half of the book is devoted to chronic rheumatism. The many pathologic features and symptoms that acute rheumatism and chronic rheumatoid arthritis have in common, such as nodules and evidence of infectious factors, are developed. Even the older osteoarthritic with his lesser degree of systemic reaction, his predominant features of degenerative processes, is regarded as expressing the same or allied causes as are present in his younger fellows. The ill-defined factor of tissue age determines in a large measure the contrasting features. This view is contrary to the belief of others who regard the hypertrophic arthritic as presenting merely the effects of age and traumata. The authors regard the pathologic changes in hypertrophic arthritis as additionally reflecting the activity of some active infective factor.

The authors believe that etiologic inquiries require recognition of the extra-articular features of chronic arthritis. Poynton would visualize the subjects of the disease as though bare of organs and composed of blood-vessels, lymphatics and nerves only, with their surrounding network of connective tissue. The "Poyntongram" of this connective tissue skeleton of the rheumatics shows deviations from normal for it is in this system that the first pathologic changes appear. Disturbances in the connective tissues are followed by interferences in the function of the "noble" organs. In joints the changes in the connective tissues are recognized as arthritis. In addition to the articular manifestations usually recognized, attention is directed to the extra-articular expressions, including muscle atrophy, which is more than that due to simple disuse, and to neurovascular phenomena. The latter are regarded as important along with irritants and

traumata in the production of osteoarthritic pathology. It is further emphasized that this connective tissue bony skeleton is not a static structure, but that there is an ebb and flow of its material components that makes it susceptible to the influence of toxic, metabolic and psychic factors.

The writers regard infectious foci as significant in providing noxious agents detrimental to the general welfare of the host, but not as as necessary first cause of the disease. A conservative attitude toward eradication of infected organs is therefore advised.

The authors' view, that metabolic studies have contributed little to the understanding of rheumatism, appears to the Reviewer to indicate a mistaken significance of the metabolic phases of rheumatism. The conventional outlook is based upon a cursory review of the fact that purine metabolism is not systemically disturbed, that lactic acid, the acid-base balance and inorganic salt metabolism are not uniformly deviated from normal, and that the carbohydrate tolerance in arthritis is not "specifically" abnormal.

In discussing protein metabolism no mention is made of its relation to the anemia, the local increases of metabolically inactive fibrous tissue and the reduction of serum albumin which the arthritic often presents. Yet these are more obvious phases of disturbed nitrogen metabolism than is a modification in the levels of circulating end products such as uric acid, and urea. The former deviations from normal represent, along with the degeneration of cartilage and modification in the matrix of bone, some of the significant changes of the protein components of the body. No mention is made of lowered cholesterol in atrophic nor of elevated cholesterol in hypertrophic arthritis; nor of the blood plasma volume increase in the atrophic as a phase of disturbed water metabolism. No mention is made of the ebb and flow of tissue water during periods of changing degrees of stiffness and swelling. However, even though the authors overlook several features of disturbed metabolism, sufficient data are presented to demonstrate the limitations of simple hypotheses regarding the etiology and nature of rheumatism.

The endocrine system is regarded as involved in greater or lesser degree in the production of some phases of the symptomatology such as the vasomotor phenomena which may underlie the predisposition of the tissues to rheumatism. No single component of the endocrine system is wholly responsible for the full picture even in so-called climacteric arthritis, in the sense that thyroid dysfunction is responsible for myxedema. The authors point out that skin involvement is so frequent as to constitute an integral part of the disease. They are optimistic as to the treatment of chronic rheumatics, having confidence that an accurate diagnosis, an avoidance of new "cures," and a reliance upon systemically operative measures will favor the recovery of the patient. Diet is handled as an individual problem for each patient. The use of grossly imbalanced rations is deprecated and the authors epitomize their whole attitude toward therapy in the following facetious but hardly critical summary: "stung by bees, giddy with histamine, sore from sulphur injections, itching from gold, short of food and threatened with wholesale dental extractions, we prefer the pleasanter forms of treatment rather than to prolong our rheumatic existence on even the most modern principles."

Brief chapters on Physiotherapy by Frank Howett, C.V.O., M.D., F.R.C.P., and on Surgical Treatment of Chronic Rheumatism by Eric I. Lloyd, M.B., B.Ch., F.R.C.P., are appended. In both of these the same perspective is maintained, emphasizing the necessity for individualized application of the various procedures at appropriate times and with due regard for the patient's general condition. C. S.

THE CEREBROSPINAL FLUID. By H. HOUSTON MERRITT, M.D., Assistant Professor of Neurology, Harvard Medical School; Director of the Cerebrospinal Fluid Laboratory, Boston City Hospital, and FRANK FREMONT-SMITH, M.D., formerly Assistant Professor of Neuropathology, Harvard Medical School; formerly Director of the Cerebrospinal Fluid Laboratory, Boston City Hospital. With a Foreword by JAMES B. AYER, M.D. Pp. 333; illustrated. Philadelphia: W. B. Saunders Company, 1937. Price, $5.00.

THE authors of this interesting monograph are ideally suited to have written it. They have spent considerable time in a study of the subject and have made worthwhile contributions to medical knowledge in this field. The monograph was not written from a single point of view. Rather have the authors presented a group of facts. Many case histories with proven diagnoses are included to illustrate the points which are made. Laboratory and clinical findings are clearly presented. There are 8 chapters, and in addition an excellent bibliography, and index of authors and subjects. The anatomy and physiology are briefly but adequately reviewed. The chemistry and pathologic physiology are thoroughly covered and many tables of data are included. The technique of lumbar and cistern puncture with clinical interpretations is well written and will prove of considerable value. The section on cerebrospinal fluid syndromes is the most extensive the Reviewer has found. The present volume might well be compared with Kafta's "Die Zerebrospinalflussigkeit" which was published in 1930. The many typographical errors found in that volume are absent in the present one. The present volume is more practical, and of course more easily used by the English-speaking portion of the medical profession. It should prove to be a constant reference for all those interested in this very important field.

I. R.

LANE MEDICAL LECTURES: THE MECHANISM OF HEAT LOSS AND TEMPERATURE REGULATION (Stanford University Publications, Medical Sciences, Vol. III, No. 4). By EUGENE F. DU BOIS, M.D., Medical Director, Russell Sage Institute of Pathology; Professor of Medicine, Cornell University Medical College; Physician-in-Chief, New York Hospital, New York. Pp. 95; 41 illustrations. Stanford University: Stanford University Press, 1937. Price, Paper, $1.50; Cloth, $2.25.

THESE lectures provide an interesting review of the classical work on heat production and direct calorimetry on man, in which the author has played such an important rôle. He points out that the presence of a causal relationship between surface area and basal metabolism is uncertain, since the basal metabolic level can be maintained over a fairly wide range of conditions of different cooling capacity. Yet the rule relating the actual observed metabolism to the total surface area (or the relatively smaller effective surface area) in various species is found to hold with a few exceptions, which are noted.

The student reader may find difficulties in a terminology which does not always conform to ordinary usage. Thus the author states "the insensible perspiration includes not only weight loss due to vaporization—but also the slight excess in the weight of carbon dioxide eliminated over the oxygen absorbed." This is not the common usage of the term "insensible perspiration" and a similar unorthodox use of terms is again exemplified when he describes Hardy's experiments on temperature sensation. He says these establish "the laws of summation which have practically ruled out the factor of facilitation." Most physiologists would state that these experiments indicated a spatial summation of sensations by a process probably actually dependent on central facilitation.

H. B.

THE MANAGEMENT OF THE PNEUMONIAS. For Physicians and Medical Students. By JESSE G. M. BULLOWA, B.A., M.D., Clinical Professor of Medicine, New York University College of Medicine; Visiting Physician and Director Littauer Pneumonia Research Fund, Harlem Hospital; Visiting Physician, Willard Parker Hospital. Pp. 508; 142 illustrations. New York: Oxford University Press, 1937. Price, $8.50.

Too long has there been a tendency in some parts of the profession to rest content in diagnosis with the attempt to distinguish between lobar and bronchopneumonia. In this book the author has collected in relatively brief form the currently accepted ideas concerning the biologic nature of the pneumonias. Adequate emphasis is given to the importance of recognizing the pneumonias as a group of specific bacterial diseases which careful bacteriologic study alone can differentiate. A useful discussion of the Neufeld method of pneumococcus typing is included. Reference is made to the work of the late Georgia Copper in identifying specifically Types IV to XXXII which in the past were customarily designated as "Group IV." Many charts and tables illustrative of the higher pneumococcus types as well as the more common types are shown. The more frequently encountered organisms, exclusive of pneumococci, that may produce pneumonia are dealt with in sufficient detail.

The management of the pneumonias is discussed as much as the subject at present allows from the standpoint of etiology. Seventy-nine pages are devoted to serum therapy and 69 to oxygen therapy. Among other topics included are general treatment, sedation, glucose, chlorides, quinine and quinine derivatives, digitalis, artificial pneumothorax and the more recently introduced rabbit antipneumococcus serum.

The format is attractive and the material presented should aid in lowering the present pneumonia mortality in the United States by diffusing the knowledge that is now available concerning the importance and feasibility of early specific diagnosis and treatment. L. C.

DER PSYCHISCHE RESTITUTIONSEFFEKT. Das Prinzip der psychisch bedingten Wiederherstellung der ermüdeten, der erschöpften und der erkrankten Funktion. (The Psychic Restitution Effect. The Principle of Restoring the Fatigued, Exhausted or Diseased Function by Psychic Influences.) By DR. MED. OTTO LÖWENSTEIN, vorher ordentl. Professor und Direktor des Pathopsychologischen Instituts der Universität Bonn sowie leitender Arzt der Rheinischen Provinzial-Kinder-Heilanstalt für seelich Abnorme in Boon. Nyon (Schweiz), Klinik La Métairie. Pp. 92; illustrated. Basel: Benno Schwabe & Co., 1937. Price, Francs suisses, 8.00.

THIS little monograph, illustrated by a number of impressive graphs, tells in plain language a story which should be interesting equally to physiologists, psychologists, neurologists and syphilologists. The pupillary reflex is recorded cinematographically under controllable conditions of light stimulation. When the pupil is stimulated for 1 second periods, with intervals of 2 seconds, the reaction decreases gradually, and eventually the pupil fails completely to react to light. Sluggishness of contraction and dilatation, increase of latency of contraction, later its replacement by initial and finally by paradoxical dilatation mark the path of the fatigue of the pupillary reflex. Seven well-characterized stages of the fatigue phenomenon are differentiated. They follow one another in regular sequence but at an individually varying time interval. The appearance of fatigue is accelerated by noxious conditions, such as blue light, by increases in the frequency of stimulation, in the duration of the single stimuli and in their strength. With each subsequent experiment the restitution time becomes longer and the quantity of residual fatigue increases. All these observations prove that in fact the central function is

exhausted and that adaptation does not play a part in the phenomenon. The pupillary reflex which has become completely fatigued and has disappeared can be restored immediately by sensory stimuli or verbal suggestions leading to fear or painful sensations or to joyful emotions. While the latter remain effective in restoring the fatigued pupillary reflex as long as they are able to produce a pleasant sensation, the stimuli accompanied by negative emotions gradually fail to elicit the phenomenon of psychic restitution. The cinematographic record shows that the reaction of the fatigued pupil to light, following a sensory stimulus, passes backward through the same seven stages which characterize the fatigue phenomenon. The "defatiguing" effect of sensory stimuli were shown also in the slightly abnormal patellar reflex, fatigued by 4 previous stimuli, in a patient with initial tabes. The effect of psychic restitution upon the pupillary reflex is present also when the reflex is partially damaged by disease. This is true in syphilitics as well as in postencephalitic Parkinsonians. The sluggish reaction in the former, the tonic in the latter regains its fast, prompt and extensive reflectory movement after psychic or sensory stimulation. No restitution effect can be produced once the pupil becomes completely fixed, even though the pupil may still enlarge the psychic influences or painful stimuli. These two phenomena, therefore, seem to be independent of each other. The degree to which pupillary function made abnormal by organic disease can be temporarily restored by psychic restitution gives an indication as to how far the function can and should be revived by treatment. Observation of a person with a Horner syndrome suggests that the appearance of psychic restitution depends on the integrity of the sympathetic innervation. It is possibly a general rule that the vegetative functions are kept alive by continuous restitution through sympathetic stimuli.

This booklet, full of well-organized facts and void of undue hypotheses, makes fascinating reading. F. L.

PRACTICAL PROCTOLOGY. By LOUIS A. BUIE, A.B., M.D., F.A.C.S., Head of Section on Proctology, The Mayo Clinic; Professor of Proctology, The Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota. Pp. 512; 152 illustrations (2 in color). Philadelphia: W. B. Saunders Company, 1938. Price, $6.50.

THE author's book is well named. From his rich experience he has written a book filled with practical and useful information concerning his special subject. Psychologic aspect of the attitude of the physician and patient in making anal and rectal examinations and in carrying out the necessary treatment are first discussed. After a description of the technique of examination, the author considers the anatomy of the anus and lower rectum. His chapter on pre-operative and postoperative care is written with a background of handling patients and might well be followed by many general surgeons who have occasion to perform operations on the lower rectum and anus. He then discusses in detail the various diseases of this region. The book ends with a chapter on diets and various prescriptions which he has found useful in his work. It is beautifully illustrated throughout and is one which should be invaluable to surgeons and internists alike, whether diagnosis or treatment of the lesions of this region is necessary in practice.

The single criticism to make of the book is that some of his recommended treatments are not those which would be found practical in the ordinary practice of proctology. For instance, in his chapter on anal fissure he recommends a more radical treatment than is usually found necessary and no mention is made of the value of oil-soluble anesthetics in this condition. In the chapter on anal pruritus his procedure of infiltration of alcohol

sufficient to produce a slough is rarely necessary. A complete and beautifully illustrated chapter on ulcerative colitis gives in detail ideas which he and Dr. Bargen have previously published.

The book is written throughout in the author's forceful manner, the use of the first person emphasizing the personal experience of the author with the diseases and treatments which he is discussing. Anyone who is at all interested in proctology will count this book as among his most valuable.

L. F.

THE POSTMORTEM EXAMINATION. By SIDNEY FARBER, M.D., Associate in Pathology, Harvard Medical School; Pathologist to The Infants' Hospital and the Children's Hospital, Boston. Pp. 201; 32 illustrations. Springfield, Ill.: Charles C Thomas, 1937. Price, $3.50.

THIS book is designed for ready reference as a guide to an adequate method of performing autopsies. Though there is already in English a very satisfactory inexpensive volume of this type, by Coman, this work will be useful to beginners in pathology and to those who perform but occasional postmortems. The material is clearly and fully presented. The drawings are of considerable aid in delineating actual technique. The incorporation of special procedures and methods for infants and children is worth while.

S. L.

VITAMINS IN THEORY AND PRACTICE. By LESLIE J. HARRIS, Sc.D., D.Sc., Nutritional Laboratory, University of Cambridge, and Medical Research Council. Pp. 242; 66 illustrations and 44 tables. Second edition. Cambridge: University Press, 1937. Price, $3.00.

IF the numerous small, semipopular books on the vitamins are to keep pace with a rapidly accumulating literature, both clinical and experimental, new editions will have to be published frequently. A second edition of this excellent compendium within two years of the first edition has, so far as possible, brought the information up to date. It tells the whole vitamin story which is always of fresh interest and uses it as a text to philosophize about the great scientists as the catalysts of scientific progress. The illustrations are many and varied, making visible the deficiency diseases in man and in experimental animals, the great scientists and lay experimenters who revealed the existence of the vitamins, and the substances themselves in their crystalline forms. The clinical applications of the vitamins are discussed at length and there is a supplementary section on dietetics that might make a good pamphlet to circulate separately. Presented originally in lecture form, the text has preserved an easy, conversational tone.

E. W.

NOT SO LONG AGO. A Chronicle of Medicine and Doctors in Colonial Philadelphia. By CECIL K. DRINKER, M.D., Sc.D., Professor of Physiology and Dean of the School of Public Health, Harvard University. Pp. 183; illustrated. New York: Oxford University Press, 1937. Price, $3.50.

ELIZABETH DRINKER, the author's great great grandmother, kept a celebrated diary with almost daily entries from 1758 to 6 days before her death in 1807. Staying much at home, mother of 9 and grandmother of 29, she naturally filled many pages of her 36 home-made volumes with accounts of family illnesses and references to the physicians who attended them. John Redman, Adam Kuhn, Rush, Shippen, Physick and other worthies live again in these pages of excerpts of medical interest from the voluminous record. Childbearing, tuberculosis, smallpox, dysenteries, malaria and yellow fever receive chief attention; but a wise selection that avoids tiresome repetition gives, as the most vivid picture of all, the domestic medicine

of a cultured household over an important transitonal period of medical history. Though the Drinkers inevitably figure prominently, the author of this volume does not hesitate to digress into general fields, such as the development of forceps and male midwives in obstetrics, Lady Montague and inoculation for smallpox, and the progress of medicine in the 19th century. (Here one might well question the author's dictum that "nowadays our large cities are healthier places than is the country.") Clearest of all emerges from her own record the doughty figure of Elizabeth Drinker herself, faithfully giving daily purges, injections, vomits, glysters and blisters to her loved ones as directed; yet with intelligence enough early to advocate vaccination over inoculation and independence enough on occasion to differ from Dr. Redman in his diagnoses. Our ancestors' constant struggle with disease and their comparative helplessness in dealing with it seldom has been more strikingly portrayed than in these humble pages. "Not So Long Ago—But What a Difference" is the amended title that will suggest itself to many a reader of this illuminating record and perhaps that is just what the author intended. E. K.

A Text-book of Medical Bacteriology. By R. W. Fairbrother, D.Sc., M.D., M.R.C.P., Lecturer in Bacteriology, University of Manchester; late Research Fellow in Bacteriology, Lister Institute, London. Pp. 437; 12 illustrations and 32 tables. St. Louis: The C. V. Mosby Company, 1937. Price, $4.50.

In the space of 437 pages it is impossible to present an exhaustive treatise on all phases of bacteriology. The author, therefore, limited himself to the application of bacteriology to medicine and public health. Not trying to save space by presenting only the well-established facts and conclusions, the author considers various controversies and problems which are confronting bacteriologists and medical men. The general plan for considering bacterial diseases was: 1, The identification of pathogenic bacteria; 2, the immunologic diagnosis of disease; 3, the detection of individuals susceptible to the disease; and 4, specific prophylaxis and therapy. The book is well printed, easily readable and beautifully bound. It is very good for beginners or those desiring an elementary treatise, but inadequate for advanced students or as a reference book. No references are cited and there are very few tables and illustrations. H. M.

A Pediatrician in Search of Mental Hygiene. By Bronson Crothers, M.D., Assistant Professor of Pediatrics, Harvard Medical School; Visiting Physician to the Children's Hospital, and to the Infants' Hospital, Boston. Pp. 271. New York: The Commonwealth Fund, 1937. Price, $2.00.

Having insight into neurology, this pediatrician realized that if adequate care was to be accorded children handicapped by nervous disorders, proper consideration must be given the educational and emotional elements of each situation. The subject matter is presented under three major headings: Mental Hygiene in the Practice of Medicine, Mental Hygiene in the Teaching of Medicine, and Towards Meeting the Pediatrician's Responsibility. In the last, is a chapter entitled, A Teaching Experiment in Action. Here are grouped children showing neurologic difficulties: 1, Those with acute diseases necessarily treated according to established methods; 2, those with "diseases that are remorselessly progressive," whose care also is a strictly medical matter; 3, children left with some residual physical or mental handicap, which necessitates the assistance of non-medical workers. The "search" is ended. The author is revealed as having understanding of the entire mental hygiene movement and one is convinced that in this realm of endeavor there is need of properly trained pediatricians.

N. Y.

THE DIAGNOSIS AND TREATMENT OF SEXUAL DISORDERS IN THE MALE AND FEMALE INCLUDING STERILITY AND IMPOTENCE. By MAX HUHNER, M.D., formerly Chief of Clinic, Genito-urinary Department, Mt. Sinai Hospital Dispensary; Attending Genito-urinary Surgeon, Bellevue Hospital, etc. Pp. 490; 8 illustrations. Philadelphia: F. A. Davis Company, 1937. Price, $5.00.

A TREATISE that has called forth a fourth edition and 21 reprintings of previous editions hardly needs more than that attention be called to the present opportunity of students of this subject. There is much new material incorporated, and a considerable part of the empirical therapy deleted. Steinach's operation is put in its proper place; as an admirer of Freud, the author gives him just due; the endocrine knowledge of today is too briefly utilized, and one looks in vain for the technique of a spermatozoa count so valuable in estimating the responsibility of the male in a sterile union. The book is exceedingly well written and well balanced, with abundant therapeutic suggestions drawn from the author's long experience in this specific field. A. R.

INTERNATIONAL CLINICS. VOL. IV. Forty-seventh Series. December, 1937. Edited by LOUIS HAMMAN, M.D., Visiting Physician, Johns Hopkins Hospital, Baltimore, with 13 Collaborators. Pp. 343; illustrated; 1 colored plate. Philadelphia: J. B. Lippincott Company, 1937.

OF the 23 articles in this volume, 9 are on surgical conditions within the abdomen; the rest are distributed over the fields of Pediatrics, Urology, Endocrinology and Infectious Diseases. The opening article by Spies and Cooper on the diagnosis of pellagra is the most interesting to the Reviewer, Its 5 case reports, characteristic of different types of the disease, and richly illustrated with 21 figures and 1 colored plate, should be of permanent value to many. E. K.

NEW BOOKS.

Alcohol. One Man's Meat. By EDWARD A. STRECKER, A.M., M.D., Sc.D., Professor of Psychiatry, School of Medicine and Graduate School of Medicine, University of Pennsylvania, etc., and FRANCIS T. CHAMBERS, JR., Associate in Therapy, Institute of the Pennsylvania Hospital, Philadelphia. Pp. 230. New York: The Macmillan Company, 1938. Price, $2.50.

Practical Proctology. By LOUIS A. BUIE, A.B., M.D., F.A.C.S., Head of Section on Proctology, The Mayo Clinic; Professor of Proctology, The Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota. Pp. 512; 152 illustrations (2 in color). Philadelphia: W. B. Saunders Company, 1938. Price, $6.50. (Review, p. 547.)

A Textbook of Hematology. By WILLIAM MAGNER, M.D., D.P.H., Pathologist, Saint Michael's Hospital, Toronto, Canada; Lecturer in Pathology, University of Toronto, etc. Pp. 395; 23 illustrations, 3 colored plates and 3 charts. Philadelphia: P. Blakiston's Son & Co., Inc., 1938. Price, $4.50.

Fractures and Dislocations for Practitioners. By EDWIN O. GECKELER, M.D., Fellow of the American College of Surgeons; Fellow of the American Academy of Orthopædic Surgeons. Pp. 252; 213 illustrations. Baltimore: William Wood & Co., 1937. Price, $4.00.

Textbook of Experimental Surgery. By J. MARKOWITZ, M.B. (TOR.), PH.D., M.S. in Experimental Surgery (MINN.), Research Associate, Department of Physiology, University of Toronto; formerly Professor of Physiology, Georgetown University School of Medicine, Washington, D. C., etc. Pp. 527; 330 illustrations. Baltimore: William Wood & Co., 1937. Price, $7.00.

Le Traitement de la Tuberculose Pulmonaire par la Tuberculine. By DR. M. JAQUEROD (LEYSIN). Pp. 43; 2 plates. Lausanne: Librairie Payot et Cie., 1937. Price, Sw. fr., 2.50.

Physicians' Vitamin Reference Book. Presenting to the Clinician a Useful Compendium of the Latest Facts about Vitamins. By the Medical Division, Professional Service Department, E. R. Squibb & Sons. Pp. 126; 10 illustrations. New York: E. R. Squibb & Sons, 1938.

Practitioners should find this handbook of great value. In not too condensed form, it covers the deficiency diseases, in both early and late manifestations, and gives in detail the food and other sources of the vitamins, and human requirements.

E. W.

The Medical Clinics of North America, Vol. 22, No. 1 (Chicago Number—January, 1938). Pp. 264; 42 illustrations. Philadelphia: W. B. Saunders Company, 1938.

St. Thomas's Hospital Reports. Second Series, Vol. II. Editors: PROF. O. L. V. S. DE WESSELOW, MR. C. MAX PATE, assisted by MR. N. R. BARRETT, DR. J. ST. C. ELKINGTON, DR. A. J. WRIGLEY. Pp. 271; illustrated. London: St. Thomas's Hospital, 1937. Price, 7s. 6d.

This second volume of St. Thomas's Hospital Reports, under the new system of including original articles reflecting recent work at the hospital, contains 23 rather brief clinical papers on a wide variety of subjects. There are also abstracts of 28 articles and a list of other publications by members of the hospital staff.

The British Encyclopædia of Medical Practice. Including Medicine, Surgery, Obstetrics, Gynæcology, and Other Special Subjects. Vol. 6. Gonorrhœa to Hydrotherapy. Under the General Editorship of SIR HUMPHRY ROLLESTON, BT., G.C.V.O., K.C.B., M.D., D.Sc., D.C.L., LL.D., Emeritus Regius Professor of Physic, Cambridge, etc. With the assistance in a consultative capacity of F. R. FRASER, M.D., F.R.C.P., G. GRAY TURNER, D.CH., M.S., F.R.C.S., JAMES YOUNG, D.S.O., M.D., F.R.C.S. (EDIN.), F.C.O.G., SIR LEONARD ROGERS, K.C.S.I., M.D., LL.D., F.R.C.P., F.R.C.S., F.R.S., and F. M. R. WALSHE, O.B.E., M.D., D.Sc., F.R.C.P. Pp. 650; 89 text illustrations and 7 plates. London: Butterworth & Co., Ltd., 1937. Price, $12 per volume.

Pulmonary Tuberculosis in Practice. A Modern Conception. By R. C. WINGFIELD, B.A., M.B., B.CH., F.R.C.P., Medical Superintendent, Brompton Hospital Sanatorium, Frimley; formerly Tuberculosis Officer, St. Thomas's Hospital. Pp. 122; 25 illustrations and 1 insert (in color). Baltimore: William Wood & Co., 1937. Price, $2.50.

Lectures on the Epidemiology and Control of Syphilis, Tuberculosis, and Whooping Cough, and Other Aspects of Infectious Disease. (The Abraham Flexner Lectures, Series No. 5.) By THORVALD MADSEN, M.D., Director of the State Serum Institute of Denmark, Copenhagen; Chairman of the Health Committee of the League of Nations. Pp. 216; 21 illustrations. Baltimore: The Williams & Wilkins Company, 1937, for Vanderbilt University. Price, $3.00.

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NEW EDITIONS.

Operative Gynecology. By HARRY STURGEON CROSSEN, M.D., Professor Emeritus of Clinical Gynecology, Washington University School of Medicine; Gynecologist to the Barnes, St. Louis Maternity, and St. Luke's Hospitals, etc., and ROBERT JAMES CROSSEN, M.D., Assistant Professor of Clinical Gynecology and Obstetrics, Washington University School of Medicine; Assistant Gynecologist and Obstetrician to the Barnes and St. Louis Maternity Hospitals, etc. Pp. 1076; 1264 illustrations including 3 colored plates. Fifth edition, revised and reset. St. Louis: The C. V. Mosby Company, 1938. Price, $12.50.

"The seven years since the last edition of this work constitute a period of unusual activity in searching out the fundamentals of gynecologic physiology and structure, and in applying such knowledge to the cure of diseased conditions. This intensive study has extended also to our therapeutic resources—old and new, medical and surgical—giving a much better understanding of their possibilities and limitations. . . . . Worthy of emphasis also is the endeavor to found every decision for operation on substantial and clearly understood reasons which justify the risk, and then to reduce that risk to the minimum by critical pre-operative examination and preparation and by effective postoperative care. . . . ." The main object of this work remains "to push the fight against disease by presenting the advances of surgery as applied to the relief of gynecologic diseases in a way which will give practical aid to the surgeon seeking help on these problems." (From senior author's Preface.)

Applied Pharmacology. By A. J. CLARK, M.C., M.D., F.R.C.P., F.R.S., Professor of Materia Medica and Pharmacology in the University of Edinburgh; formerly Professor of Pharmacology in the University of Cape Town, and later in the University of London. Pp. 678; 83 illustrations. Sixth edition. Philadelphia: P. Blakiston's Son & Co., Inc., 1938. Price, $5.00.

Practical Bacteriology, Hæmatology and Animal Parasitology. By E. R. STITT, M.D., Sc.D., LL.D., Rear-Admiral, Medical Corps, and Surgeon-General, U. S. Navy, Retired; formerly Associate Professor of Medical Zoölogy, University of the Philippines; PAUL W. CLOUGH, M.D., Chief of Diagnostic Clinic, Johns Hopkins Hospital; Associate in Medicine, Johns Hopkins University, etc.; and MILDRED C. CLOUGH, M.D., formerly Fellow in Bacteriology and Instructor in Medicine, Johns Hopkins University. Pp. 961; 208 illustrations (4 in colors). Ninth edition, rewritten, revised and enlarged. Philadelphia: P. Blakiston's Son & Co., Inc., 1938. Price, $7.00.

The Compleat Pediatrician. Practical, Diagnostic, Therapeutic and Preventive Pediatrics. By WILBURT C. DAVISON, M.A., D.Sc., M.D., Professor of Pediatrics, Duke University School of Medicine, and Pediatrician, Duke Hospital, etc. Pp. 275. Second edition, completely rewritten for the use of medical students, internes, general practitioners, and pediatricians. Durham, N. C.: Duke University Press, 1938. Price, $3.75.

"This second edition, which has been so completely revised that it might be called 'The Compleater Pediatrician,' was written because of the additional pediatric information which has accumulated during the past four years. The great usefulness of pediatric yearbooks and periodicals is realized as 'only a maker of books can appreciate the labours of others at their true value' (Osler), and they have been freely used. However, they merely record the changes in pediatrics, while this revision is an effort to correlate these newer advances with the pre-existing knowledge, and to present an up-to-date digest. . . . . The present edition is an effort to compile and record briefly those *practical* pediatric facts, which though essential, usually slip from memory; it is an attempt to combine in one volume, the information usually found in several, which should be consulted for more complete study. . . . . The hope is expressed that this book may serve as 'a ready reminder' to be carried, like a stethoscope, in a physician's pocket or bag (see Chapter XII) to jog his memory on possibilities, but it cannot do his thinking for him." (From the author's Preface.)

PROGRESS
OF
MEDICAL SCIENCE

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF
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ECTOPIC PREGNANCY.

WHILE ectopic pregnancy is no longer the curiosity it was a generation or two ago, it still holds much interest for the gynecologist as well as for the general practitioner. The treatment of the condition has become well standardized in the average case but in some of the unusual cases there is still room for discussion. Likewise the diagnosis of the case which presents a textbook picture seldom eludes the average practitioner, but in the atypical cases, and there are many of them, the attending physician's diagnostic ability may be severely tested. We do not definitely know why these pregnancies develop outside of the uterus but the theory which has been advanced by Frankel and Schenck[2] is at least interesting. Along with other observers they have demonstrated healthy endometrial tissue in tubal lumina whether or not they were the site of pregnancy. They have found such tissue present at the site of a pregnancy in 87.5% of cases where they have made a careful search and believe that it is present at the outset in 100% of the cases. In 1 case, they found endometrial glands in the decidual tissue, which they believe proves that the decidual reaction was caused by the response of the endometrial elements and not the tubal structure itself. This ectopic endometrial tissue was found in 1 out of 204 normal cases, an incidence of 0.5% which corresponds to the ratio of ectopic to intrauterine pregnancy. According to their theory, all ectopic pregnancies, tubal or otherwise, occur because of nidation of the fertilized ovum in a locus of ectopic endometrial tissue to which the ovum is chemotactically attracted. The fate of the gestation depends upon the amount of endometrial tissue present to undergo the decidual reaction and upon the depth of penetration of the ovum beyond the borders of this decidua. It has been repeatedly stated that a tubal pregnancy may lose its position in the tube and implant itself secondarily elsewhere, con-

tinuing its growth in the new site. They do not believe that this is possible because the embryo depends upon the maintenance of a free flow of maternal blood around its chorionic villi. When the trophoblast is confined in decidua, the embryo is nourished, but when the villi break their bounds, they become embedded in blood clot and the embryo is in a short while asphyxiated. They state that it is impossible for an embryo once surrounded by coagulated blood to extricate itself when deposited in a fresh place and recommence its development. Whether tubal rupture or tubal abortion occur the fate of the embryo is sealed from the moment the perifetal coagulation starts. Hence the existence of an ovarian pregnancy, an abdominal pregnancy, or an intraligamentous pregnancy cannot follow on its extrusion from the tube but exists because it begins its development primarily in these sites.

Diagnosis. In discussing the diagnosis of tubal pregnancy, Mathieu[7] is of the opinion that the typical history of a missed menstrual period, sharp lancinating pain in the lower part of the abdomen, followed by dizziness, weakness and faintness, soreness in the abdomen, and bleeding from the vagina, represents only a small percentage of all the cases of tubal pregnancy. The others, not typical, are at times very difficult to diagnose. There are patients with symptoms and complaints so minor or so bizarre that the physician may actually wonder whether or not there is anything wrong at all. There is no doubt that many cases go undiagnosed and that the effects go unnoticed. For those who like the finer points of diagnosis, he presents 8 types of pain which are met in this condition, all explainable on a pathologic basis: 1, Acute lancinating pain coincident with rupture of the tube; 2, dull, constant pain associated with stretching and slow tearing of the tube before rupture; 3, crampy, almost constant pain caused by peristalsis of the tube and dilatation of the distal end of the tube during a tubal abortion; 4, soreness and tenderness of the entire abdomen caused by irritation of the peritoneum from the escaped blood; 5, phrenic or shoulder pain produced when the blood gets high in the abdominal cavity, under the diaphragm, and irritates the phrenic nerve endings (this pain is felt on either or both sides of the neck); 6, pain elicited by the deep muscle resistance that results when the palpating fingers sink deeply enough to cause pressure on the parietal peritoneum. When there is free blood in the abdominal cavity, palpation of the anterior abdominal wall is almost pathognomonic. The abdomen is usually not distended. There is generalized pain or soreness over the entire abdomen and with fairly light palpation the fingers will sink part way into the abdominal wall without resistance, only to be met by a rather doughy resistance as the fingers sink deeper. This tenderness is quite unlike that of the acute firm resistance and tenderness one finds in acute appendicitis with peritoneal involvement; 7, pain produced by moving the cervix or fundus; 8, generalized pelvic tenderness and pain produced by the palpating fingers. It should be realized that all of these pains are not present in every case but their enumeration should make us think of them. To the Reviewer, the pain produced by motion of the cervix during pelvic examination, while not stressed much in most textbooks, is of extreme diagnostic importance and is seldom absent. This pain is usually excruciating and is rarely found except in ectopic pregnancy.

In regard to pregnancy tests such as the Aschheim-Zondek or any of its modifications, it should be remembered that a positive test means that there is living chorionic tissue present, hence the test can be positive even when the fetus is dead. A negative test merely means that there is no living chorionic tissue present, therefore the test will not exclude the diagnosis of ectopic pregnancy. Moreover the test, if positive, gives no indication as to whether the pregnancy is intra- or extrauterine. In regard to a diagnostic aspiration of the cul-de-sac, Mathieu does not consider it entirely harmless and he does it only when the presence of fluid in the pelvis is obvious, under which conditions it is often an important diagnostic procedure. The sign described by Cullen is the presence of an ecchymosis in the tissues of the umbilicus. There must be not only an actual hernia but also some break in the integrity of the peritoneum at this site so that the blood can actually reach the subcutaneous tissues. He has found the sign to be extremely rarely present and that is also the experience of the Reviewer. (The Cullen sign is rarely seen in early cases.) The urobilinogen and icterus index tests are of value in determining the presence of a hematoma or of blood in the process of absorption and hence might point to a ruptured ectopic pregnancy. The blood sedimentation test is of little direct diagnostic value, a rapid rate usually rules out ectopic pregnancy while a slow rate is infrequent in the presence of a pelvic abscess or salpingitis. He has used hysterosalpingography in several cases as an aid in diagnosis with practically 100% correct diagnoses. He has been able to visualize a tubal abortion and has established what seems to be a pathognomonic Roentgen ray sign for a tubal pregnancy in the midportion of the tube. In cases of tubal pregnancy aborting from the distal end of the tube, the injected oil enters all the crevices between the aborting pregnancy and the walls of the distal end of the tube in such a way that it literally drapes itself about the mass and allows the oil-covered mass to be visualized by the Roentgen rays. In his cases of tubal pregnancy in the midportion of the tube, the injected oil went down to the site of the pregnancy and, because this site was well sealed off, ended abruptly and showed in a characteristic shadow. While this procedure should not be done routinely, if done carefully it should be harmless and if both tubes fill normally, at least ectopic pregnancy can be ruled out. This test should be of particular value in differentiating ectopic pregnancy from the internal hemorrhage associated with a ruptured ovarian follicle or corpus luteum, in which differentiation no other tests are of much assistance.

Buschbeck[1] states that the diagnosis of ectopic pregnancy presents no difficulty when the usual signs of a ruptured gestation sac are present such as internal hemorrhage, hematocele and peritoneal shock. In those cases in which the pregnancy runs a more chronic course there may be considerable difficulty in diagnosis. In such cases the menstrual history may be the only diagnostic sign of importance. He has investigated the history in 143 cases and found that in 141 of them it conformed to one of three types. In the first type the history is only that of amenorrhea and there were 17.5% of the cases in this group. The second type, which was that shown by over half (58%) of the patients, consisted of a period of amenorrhea followed by continuous bleeding. In the third type, comprising 23.1% of the cases, the history was that

of an atypical period at approximately the usual time, either more or less bleeding than usual, then a free interval followed by continuous bleeding. Therefore in any patient who exhibits any one of these three types, particularly if accompanied by pelvic discomfort, a pelvic examination should be done and if no definite diagnosis can then be made, the patient should be kept under observation until the diagnosis becomes clarified.

Another study of the diagnostic value of the menstrual history based on a series of 153 cases has been made by von Graff and Brown.[12] In 9% of the cases irregular bleeding over a period of several months barred definite conclusions. In 38% the bleeding followed definite amenorrhea, but in 53% there were no previous menstrual disturbances. In these cases, the bleeding started either during the intermenstruum or at the expected time, presumably as a normal period, but was unduly prolonged. The latter type of bleeding is very misleading, especially if there are no local symptoms. Observation of the bleeding often gives definite clues. At the onset there may be copious bleeding with the expulsion of clots and tissue but this may occur with intrauterine abortion and only histologic examination can differentiate between the two conditions. In uterine abortion, the blood remains red but in ectopic pregnancy the discharge gradually assumes a dirty brown color which is almost pathognomonic. As important as the color is the duration of the bleeding. In intrauterine abortion, since the pregnancy is not far advanced, the flow usually stops with the spontaneous completion of the miscarriage or after bed rest and the use of oxytocics, but in tubal abortion the discharge goes on regardless of treatment. The hemoglobin and red cell count do not often suggest intraäbdominal bleeding but the white cells are frequently increased to such an extent as to suggest infection which explains the frequent erroneous diagnosis of acute pelvic inflammation. The temperature may or may not be elevated but is seldom over 101° F. but the pulse rate is high. This is to be expected with marked anemia or shock but may be present even when the patient's general condition is good due to peritoneal irritation by the blood in the peritoneal cavity.

In ectopic pregnancy, according to Siddall and Jarvis,[10] incorrect diagnoses occur in from 15 to 40% of the cases and they recommend the performance of uterine curettage as an aid in making the diagnosis. It will be remembered that in intrauterine pregnancy the chorion forms in the uterus while in ectopic pregnancy only decidual tissue is found there, the chorion, being of ovular origin, will form wherever the ovum lodges. In a series of 38 cases of proved ectopic pregnancy with available specimens of endometrium, intact decidua alone was present in all cases with abnormal bleeding of 10 days or less and in a considerable proportion of those with more prolonged bleeding. The absence of decidual reaction is not reliable evidence against ectopic pregnancy, but if chorionic villi are also absent, the findings may be of value in ruling out uterine abortion as a cause of bleeding. The performance of such curettage in a suspicious case is not unduly dangerous and the finding of intact decidua without chorionic villi is strong presumptive evidence of the existence of extrauterine pregnancy. (The diagnosis can usually be arrived at by other means and hence diagnostic curettage is rarely necessary.)

It is not unusual in certain cases of intrauterine pregnancy that have exhibited spotting or bleeding, accompanied by some pain in the lower abdomen, for the surgeon to subject the patient to a laparotomy because of the fear of the existence of an ectopic pregnancy and it must be admitted that in some cases this is the safest plan to follow. In such instances Hope[5] feels that peritoneoscopy is of value for by this procedure we have a method of actually seeing the uterus, tubes and ovaries. It can be done under local anesthesia and requires but 24 hours of hospitalization. Should the peritoneoscope determine that the pregnancy is within the uterus, the danger of aborting is less likely than following a laparotomy. The patient may return home for expectant treatment, with a saving of several weeks of hospitalization for postoperative care and of much discomfort, not to mention conservation of finances. If, on the other hand, an ectopic pregnancy is seen, immediate laparotomy is done and both the physician and the patient are saved time, worry and the risk of delay. In the performance of peritoneoscopy, the technique which he recommends consist of preparing the abdomen as for laparotomy. The bladder must be catheterized immediately before the examination because a full bladder may obscure the view of the pelvis. Local anesthesia, using 1% novocaine, is infiltrated in a wheal formation, starting at a point in the midline about 4 cm. below the umbilicus and taking in all layers down to and including the peritoneum. Should there be a scar from a previous laparotomy, the site for entering the abdomen with the trocar is chosen well away from it, to avoid any adhesions that may be present. After anesthesia is established, a stab wound, 1 cm. long, is made through the skin and rectus fascia. A small trocar is inserted into this and pushed through the peritoneum into the abdominal cavity. A pneumoperitoneum is then created by injecting air into the peritoneal cavity through the trocar using a small manometer bulb. The small trocar is withdrawn and the trocar sheath inserted into the peritoneal cavity through the stab wound with safety, as the intestines are held down by a cushion of air. The trocar point is removed from the sheath and a visual telescope is inserted. Any air that has escaped is now replaced, as air is essential for good visualization as well as a means of displacing the viscera. A general rapid survey of the peritoneal cavity is then made, going completely around the clock. The patient is then placed in the extreme Trendelenburg position which allows the intestines to fall back out of the pelvis and a detailed examination of the uterus and adnexa may be made. This is greatly facilitated in many cases by an assistant placing two fingers in the vagina and manipulating these organs. By this means the uterus can be pushed up into view if dropped far back in the pelvis, a prolapsed ovary brought into sight, and adhesions and fixation of the uterus demonstrated. On completing the examination, the patient is replaced in the horizontal position, the air is allowed to escape from the peritoneal cavity through the instrument and the latter is removed. If an ectopic gestation or hemoperitoneum is found, immediate operation is then performed. The skin is again prepared, new drapes are placed and the stab wound is incorporated in the usual laparotomy incision. If on the other hand there is no indication for immediate surgery, a single stitch or clip is placed in the stab wound. The patient is sent back to bed, care being taken that she stays in the

prone position for 12 to 24 hours to prevent shoulder pain. There is no distress from inflation of the abdominal cavity or from any small amount of air that may be left after the procedure unless the patient assumes the upright position, in which event she will probably have shoulder pain from irritation of the diaphragm by the air. After 24 hours any air that has been left in the abdominal cavity will have been absorbed. If on the first attempt at visualization a frank hemoperitoneum is seen, the diagnosis is self-evident. While hemoperitoneum is not always due to a ruptured tubal pregnancy, it definitely justifies the institution of operative treatment.

Advanced Ectopic Pregnancy. In presenting a case of ectopic pregnancy that went 49 weeks before operation was performed, Roques and Winterton[9] review the literature on the subject and comment on the difficulty in diagnosis in such cases. After diagnosis has been made they believe that operation should be done as soon as possible and not delayed with the idea of obtaining a viable child. At operation, the important factor is the disposition of the placenta. They do not favor marsupialization with its long convalescence and resulting incisional hernia. If the placenta is found attached to the uterus or omentum, it should be removed, taking the uterus or omentum with it if hemorrhage is severe. If, however, the placenta is attached to intestines, they believe it is better to leave it *in situ* and close the abdomen without drainage. The placenta will be gradually absorbed over a period of about 12 months.

In reporting a series of 10 cases of *secondary abdominal pregnancy*, Reel and Lewis[8] state that the consensus at the present time is that most, if not all, abdominal pregnancies are secondary to tubal gestation. The mechanism by which the abdominal implantation takes place may be tubal rupture or tubal abortion. Before such a case can be considered as a primary abdominal pregnancy, the tubes, ovaries and broad ligaments must be demonstrated as normal; there must be no evidence of penetration of the broad ligaments by the fimbriated ends of the tubes and there must be no evidence of interligamentary rupture of the tubes. In this series which they report, all admittedly secondary pregnancies, there was not always a history of a missed period before the onset of illness but pain was universally present. Constipation which increased gradually from the onset of the present illness was the outstanding gastro-intestinal complaint. Bleeding occurred in 6 cases and was usually preceded or accompanied by cramp-like pains. The diagnosis of secondary abdominal pregnancy rests upon the history plus findings indicative of pregnancy such as softening of the cervix, bluish discoloration of the cervix, breast changes and so forth, and the presence of a pelvic mass. In handling such cases, if there is no sudden intraäbdominal catastrophe, the patient should be put to bed for rest, and a complete check of her blood, urine and general condition should be made. Transfusion before, during or after operation should be decided upon, depending upon the grade of anemia present and the urgency of operation. The surgeon must decide as to the most favorable time for operation, whether at the time the diagnosis is made, when labor begins or when fetal death occurs, remembering that at the latter time the placental blood supply is diminished with consequent lessened danger of hemorrhage. In regard to the method of handling

of the placenta, they used marsupialization almost exclusively since they believe that drainage is a safeguard. Even though the removal of the gauze is rather painful, the pressure of the gauze pack is sufficient to control most of the bleeding and acts as an indicator of any especially active hemorrhage and affords drainage of any infection present. In removing the drain, they begin the first postoperative day and remove it fractionally in six days.

Hysterography has been employed by Greenhill[3] as an aid in the diagnosis of abdominal pregnancy. While such gestations are not often encountered and even when present are frequently not suspected, he believes that when such a diagnosis seems to be correct, injection of iodized oil into the uterus is not only a simple and relatively harmless procedure but presents absolute evidence of the presence of a pregnancy outside of the uterine cavity. A roentgenogram taken of an abdominal pregnancy taken without previous injection of an opaque substance into the uterus frequently shows a dead or live fetus in an abnormal location, but it does not prove that the fetus is outside of the uterus. Likewise in cases in which the fetus is dead and repeated attempts to induce labor by medicinal and mechanical means fail to bring about expulsion of the child, it is advisable to perform hysterography and occasionally one may be surprised to find an abdominal gestation. If the child is alive it might be dangerous to inject solutions into the uterus. In the case of abdominal pregnancy which he reports he believes that it was an ovarian pregnancy for the reasons enumerated below: 1, The uterus was entirely normal both on the Roentgen ray plates and at the time of operation. There were no scars on it and the only adhesions on it were from the fetal sac and these were slight; 2, both tubes were intact for their entire length; 3, both broad ligaments were entirely normal; 4, a careful search at the time of operation failed to reveal the right ovary; 5, the pregnancy mass was almost entirely free from adhesions. In advanced tubal gestations there are usually many adhesions and the placental attachment is often an extensive one; 6, the right tube coursed over and in front of the fetal sac as is usual in most ovarian enlargements; 7, microscopically, there was a layer of cellular tissue that resembled ovarian cortex and adjoining it was definite chorionic tissue.

Newer Aids in Treatment. Reporting from Knaus' Clinic in Prague, Hajek[4] extols the great value of *autotransfusion* in cases of ectopic pregnancy with severe internal hemorrhage. They have used the apparatus devised by Knaus, which is quite simple, in 22 cases giving blood in amounts varying from 250 to 1700 cc. The advantages of autotransfusion are the saving of valuable time by not having to type donors or test for cross-agglutination, the possibility of giving the patient large amounts of her own blood and the impossibility of transmitting any disease from donor to recipient. One of the point which is usually emphasized in this procedure is the addition of some solution such as saline or citrate to prevent clotting of the blood after it has been removed from the abdomen. Hajek states that such a procedure is harmful and unnecessary, since it reduces the vitality of the blood cells and, moreover, the blood removed from the abdomen following an ectopic pregnancy will not clot. Of course large clots are usually found in the abdomen in these cases, but the point which he makes is that the blood

which remains as liquid blood in the abdomen will not clot after it has been removed. This fact is not generally known but he is absolutely sure of this fact and has kept such blood for a week without any evidence of clotting. The Reviewer, after reading this article kept some blood from a case of ruptured ectopic gestation for several weeks and it remained entirely liquid throughout that period, so his personal experience corroborates the statement of Hajek. Why such blood does not clot is not certain, but it is believed that it has been defibrinated by the intestinal movements. If fresh blood is added to it, clotting will occur and this should be remembered because if non-citrated blood from the abdominal cavity is being transfused, it should not be mixed with donor blood. The fibrinogen content of blood from the abdomen varies from 0.018 to 0.09% as against a content of 0.2 to 0.4% for normal blood.

Spinal anesthesia is considered by Koster and Sheinfeld[6] to be an important factor in minimizing the trauma of the operative procedure in a woman already damaged by a severe intraäbdominal hemorrhage. Maximal relaxation is afforded which insures easy, speedy operating with minimal tissue trauma. The fear that many of these patients already having a low blood pressure are not fit for spinal anesthesia because of its depressing effect on pressure, is entirely unwarranted in their opinion. The Trendelenburg posture insures sufficient gravity drainage back to the heart to prevent its contraction on empty chambers, no matter how complete the peripheral and splanchnic dilatation of vessels may be. Although there were only 2 cases in their series in which no blood-pressure reading could be obtained they have operated upon 12 other cases for various types of internal hemorrhage in which blood pressures were so low that a reading was unobtainable. These experiences in extreme cases, besides a familiarity with the uselessness of blood-pressure readings as a criterion of a patient's condition during operation under spinal anesthesia gained in over 10,000 laparotomies, convinces them that ectopic pregnancy is not only no contraindication to the use of this type of anesthesia but that it is a very satisfactory method to use in such cases. In spite of their enthusiasm it will probably be some time before the large majority of gynecologists will accept this as the method of choice since open-drop ether, with its stimulating action, has proved to be so satisfactory in such cases.

Fertility After Ectopic Pregnancy. Since an ectopic pregnancy may recur on the opposite side, Strassmann[11] investigated the question as to whether it was worth while to save the other tube at the time of operation. Of a series of 142 patients, there were 42 who were sterile or could not for various reasons be expected to become pregnant after operation. In the remaining 100 cases subsequent pregnancy was at least theoretically possible and of these he was able to find the subsequent history in 84 cases. Of this number, 31 (36.9%) became pregnant later, 28 (33.3%) having intrauterine pregnancies and 3 (3.6%) having a recurrent extrauterine pregnancy. Forty-seven intrauterine pregnancies occurred in these 28 patients and 32 of these resulted in full-time deliveries with 29 living children; there were 3 stillbirths. The mother of 2 of the still-born babies had syphilis. In this group of intrauterine pregnancies there were 4 premature deliveries, 10 miscarriages and 1 hydatidiform mole. There were some patients whose

other tube was more or less affected and without an insufflation test it is almost impossible to tell whether the remaining tube is patent or not. Therefore there were undoubtedly some patients in this group who are practically sterile because of changes in the remaining tube. On the other hand, there may be a considerable number of patients in this group with a patent tube who did not desire to become pregnant again and who used contraceptive methods to prevent it. Concerning the surgical procedure employed, usually only the pregnant tube was removed and both ovaries were left. If one ovary has to be removed together with the tube, the chances for subsequent pregnancy do not seem to be much less, at least not 50% less. Of the 32 full-time pregnancies, 21 occurred in 14 patients with both ovaries left, while 11 occurred in 7 patients with only one ovary left. There is widespread opinion among laymen, and even among some physicians that the right ovary delivers only one sort of ovum (only male or female) and the left ovary the opposite. That this is not true was evidenced by the fact that there were 3 boys and 1 girl in cases in which the right ovary was preserved and 3 boys and 2 girls in cases in which the left ovary was preserved. One patient who had her left ovary removed had a boy and a girl later, both ova having come from the right ovary. It seems that tubal pregnancies occur more frequently on the right side, according to various statistics. An explanation which is not mentioned in the literature, based on an observation which Strassmann has made is as follows: A larger percentage of people are accustomed to sleeping on the right side than on the left, probably because lying on the left side sometimes causes uneasiness because of pressure on the heart. In many cases the ovum, after the bursting of the follicle, moves freely and passively in the abdominal cavity; therefore, since it would follow the law of gravity, it would appear that it might more often drop to the right side on which most people sleep. This explanation is, of course, purely speculative but it is interesting. The conclusions drawn from this report are that since the probability of intrauterine pregnancy after one ectopic pregnancy is about 10 times greater than the probability of another ectopic pregnancy, conservative surgery is advisable in order to preserve fertility. Only if the other tube is severely diseased should it be removed. In this connection it is well to remember, at the time of operation, that the non-pregnant tube undergoes certain acute changes in more than 50% of tubal pregnancies, such as swelling, redness and peritoneal friction, produced by hematomas. Such changes do not indicate removal of the tube as they usually disappear and do not interfere with subsequent fertility.

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DERMATOLOGY AND SYPHILOLOGY.

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CARBOHYDRATE AND WATER METABOLISM AND THE VITAMINS IN SKIN INFLAMMATION (DERMATITIS)

IT has become increasingly apparent as knowledge of the chemistry of cutaneous processes has developed that cutaneous inflammation, and particularly inflammation due to infection, is greatly influenced if not actually conditioned by fundamental metabolic processes, including those involving carbohydrate, and water balance. In this review, an effort is made to collect the recent general and specific contributions on these two factors, and to add to them certain comment on vitamin functions wherever recent knowledge tends to suggest that they affect cutaneous inflammatory processes.

The Influence of the Carbohydrate. Oldest in point of time are certain contributions by Kendall[31a,b,32] and his associates pointing towards an influence of orally ingested carbohydrate upon vasomotor instability mechanisms which are clinically important predisposing factors to a wide variety of inflammatory reactions. Before proceeding to discuss the rôle of intestinal carbohydrate dyspepsia in skin inflammatory reactivity, a fundamental distinction should be drawn between the action of carbohydrate introduced *per os* and carbohydrate introduced parenterally and particularly into the blood stream. An investigation of this distinction as reflected in skin infections, was first conducted by Pillsbury and associates. Pillsbury and Kulchar,[55] after developing strains of staphylococcus which produced a "standard" or constant necrotizing ulcer in rabbits, succeeded in showing that the *parenteral* administration of glucose in 7.5 gm. doses per kilo every 12 hours had no effect on experimental staphylococcic skin infection, or seemed even to favor their healing. But when the dose of glucose was increased to 15 gm. per kilo in 24 hours and given at intervals of 4 hours, a very marked increase in the extent and severity of the experimental skin infection took place. This, however, likewise followed intraperitoneal injection of sodium chloride solution of the same tonicity as the sugar and in similar amount. This was the first intimation in their work that the influence of carbohydrate on skin infections is at least as much a function of its effect on water balance as on the glucose content of tissues. The findings of Craven[12] on the arsphenamine tolerance of dogs, which on a carbohydrate diet is impaired by the development of a hepatitis, led one of us (JHS[63]) to suggest that at least part of the effect of ingested carbohydrate on skin inflammation can conceivably be by way of its influence on the bacterial content of the intestinal tract with associated

toxic liver injury. To this belief the further work of Pillsbury and Sternberg[56a,b] on skin infection in dogs afforded material support. They found that the course of experimental skin infections is more severe on a high carbohydrate diet than on a high fat diet, or fasting. They noted foul stools and diarrhea in the carbohydrate-fed animals. At this point theorization was reënforced as previously intimated, by the observations of Kendall who, in 1926, described a clinical syndrome of "intestinal carbohydrate dyspepsia" in man, with subsequent important observations on its bacteriology. It is this syndrome or an approximation to it which supplies a part of the vascular background for certain tendencies to skin inflammations.

Its close resemblance to the constitutional symptomatology of the rosacea complex in cutaneous disease, for example, the basis of acne rosacea, a pyogenic infection on a vasodilational base, was discussed by Stokes and Beerman.[64] The explanation drawn by them from the Kendall syndrome is as follows: A high carbohydrate intake in the presence of *Welch bacillus* and *B. mucosus capsulatus* in an intestinal content of low pH, favors the formation of histamine-like substances, whose toxicology as described, for example, by Cushny,[14] quite strikingly reproduces both the cutaneous vasomotor and general constitutional aspects of the rosacea complex. It would appear that the work of Kendall and his associates makes it possible to link the ingestion of carbohydrate in susceptible subjects with a histamine body absorption mechanism to provide a vasomotor and particularly vasodilational background for the localization and development of inflammatory processes on the skin. Since Kendall's work, Althausen, Gunnison, Marshall, and Shipmann[1] have conducted investigations tending to confirm both the clinical syndrome and the bacteriologic characteristics of "intestinal carbohydrate intolerance." They specifically name the development of vasomotor instability as a characteristic feature, and the other enumerated symptomatic details are identical with the findings both of Kendall as to intestinal carbohydrate intolerance, and of Stokes and Beerman on the constitutional background of the rosacea complex. Owles[50] states that inadequate pancreatic function and lack of intestinal diastase are not responsible for the symptomatology, and that the changed motility of the small intestine is probably by exclusion one of the most important factors.

So much, then, for carbohydrate by mouth. The next group of effects which carbohydrate may have on the course of inflammation concerns its influence on the hydration of tissue. Pediatricians, as Földes[21] points out, have clearly recognized the influence of high carbohydrate intake on water retention as the direct opposite of that of the protein-rich diet. Bischoff and Voit,[4] Moraczewski,[47] and Meyer-Bisch[44] have shown that in adults on a diet rich in carbohydrate, retention of both water and minerals develops. A recent summary by Hoelzel[28] points out the relation of carbohydrate restriction to resistance to colds, and cites the pertinent literature. Atchley, Peters and Kydd (*cf.* Cantarow[5]) have identified the effect of carbohydrate restriction as due to a pronounced loss of base (chiefly NaKCl). Since the sodium chloride of the skin is a leading element in its water retaining power, this explanation of the dehydrating effect of loss of carbohydrate seems particularly applicable to skin conditions. Földes, quoting Schiff,[59] points out that in experimental animals in which dehydration has been produced by a dry diet, no inflammatory reaction follows artificial

infection, and although the animals die, this occurs without any such pathologic-morphologic changes in the organs as are common after infections under ordinary conditions. It is noteworthy that dehydration leading to an entire absence of inflammatory reaction can be produced if the dry diet consists mainly of proteins, but not otherwise. On a high carbohydrate diet, even if it is dry, sufficient water is apparently retained to prevent extreme dehydration. Schiff makes it quite clear that the usual signs of inflammatory reaction to infection are the ones which are absent if the water content of the tissues is inadequate, though intoxication and death from the infection may nonetheless take place. Thus inflammatory response to infection can, by way of tissue hydration, be markedly affected by carbohydrate intake.

Dealing with the skin as such, Tobler and Bessau,[72] and Klose[33] observed the special significance of the skin as a water depot in infants and small children as compared with adults, and pointed out the fact that exclusive carbohydrate nutrition produces marked retention of water in the skin.

The work of Pillsbury and Kulchar, previously referred to, approaching the subject directly in the experimental animal, took the first step towards elucidation of a variety of seemingly contradictory results. It has been pointed out on several occasions, notably by Tauber[69] in the treatment of furunculosis, and by Crawford and Swartz[13] in the treatment of acne, that a high carbohydrate intake *per os* and even the intravenous injection of moderate amounts of glucose stimulated recovery in pyogenic infections in man. When Pillsbury and Kulchar found in the rabbit that what might be called a large but not excessive dose of glucose intraperitoneally tended to promote rapid healing of skin infections in rabbits and that, when the dose became excessive, a marked increase in the extent of the skin infection occurred, their control gave them the clue to the explanation. The increased severity of the infection could not be ascribed to increased glucose as such, because the effect could be reduplicated by the administration of hypertonic sodium chloride intraperitoneally. They were, therefore, disposed to attribute the unfavorable influence of large amounts of parenterally introduced glucose on skin infections, to its effect on the water balance of the skin rather than its action as carbohydrate as a nutrient material for microorganisms. The unfavorable influence of glucose *per os*, a very different matter, is perhaps limited to those human beings or animals in whom a vasomotor instability factor is induced through varying grades of "intestinal carbohydrate dyspepsia" with their accompanying bacteriologic and intestinal absorptive effects.

A theory such as the foregoing is too simple for so complex a group of reaction possibilities. That the whole question of the rôle of carbohydrates in skin inflammation still lacks some essential clarifying linkage, was apparent from Pillsbury and Kulchar's inability to demonstrate a parallel in experimental animals between the glucose and water content of the skin. It is apparently not glucose as such which plays the unfavorable rôle in producing increased susceptibility of tissue to inflammation and infection.

Some indication as to this intermediate factor has been afforded by the very important work of Menkin[42a,b,43] and his associates. Pillsbury,[54] following the lead of Leake, Hall and Koehler, has pointed out the influence of *lactic acid* as a vasodilator, and rated it as important

in the production of skin erythema. Menkin, through a series of extremely illuminating experiments on the production of pleural inflammation by turpentine injection, has apparently succeeded in showing that the lactic acid formed or present determines the characteristics of the inflammatory process at a site of irritation or infection (?), and that the formation of this lactic acid is a function of the disturbance of the local carbohydrate metabolism. This influence is at least in part exerted through the pH of the exudate in that a neutrophil response occurs in a neutral or slightly alkaline exudate, but that macrophages appear as the pH falls below 7.0, and the neutrophils previously present degenerate, producing pus.

It would thus appear that local inflammatory processes are profoundly influenced by the local carbohydrate metabolism insofar as it involves a free or abundant production of lactic acid from the locally available carbohydrate. It is this lactic acid production which determines to a considerable degree the pathologic characteristics of the locally excited inflammatory reaction.

To summarize, then, the influence of carbohydrate upon inflammations in the skin takes apparently a three-fold direction. It may influence them through the gastro-intestinal tract, in which intestinal carbohydrate intolerance may produce a pathologic picture leading to vasomotor instability and localized vasodilation (*e. g.*, the face) on which infective processes easily take root. It may, and does profoundly influence infective processes in the skin through hydration, for a high carbohydrate intake leads to water retention in tissue; and carbohydrate restriction leads to dehydration with corresponding disappearance of at least the inflammatory manifestations accompanying infection. Thirdly, the carbohydrate content of tissue influences inflammatory processes through the formation of lactic acid as a sequel of local inflammatory pathologic change, and with this formation of lactic acid marked change in the cellular and protective leukocytic reaction, incident on the change in pH, occurs.

The as yet unexplained favorable effect of intravenously administered glucose on local skin infections in man and animals remains a distinct gap in our equipment for interpreting the rôle of carbohydrate in cutaneous inflammation. It is conceivable that its favorable influence in moderate amounts is effected through assistance rendered the liver in dealing with circulating intoxicative agents and in the production of antibodies. It should be pointed out also that if markedly hypertonic solutions of glucose are, as is customary, employed (20 to 50%), the intravenous administration of the glucose itself will be an effective dehydrating agent. It is not even necessary that the glucose be markedly hypertonic, for as it is eliminated rather than utilized it will carry fixed base with it, leading to a loss of water by the tissues, including the skin, and hence a more favorable reaction in local inflammations.

There remains to be collected a group of less easily classified observations on carbohydrate factors in skin inflammatory processes. It has been noted by Ferannini[18] that the injection of parathyroid hormone is followed by a reduction ranging from 13 to 56% in blood sugar and an increase in carbohydrate tolerance in normal and diabetic subjects. Pillsbury and Sternberg[56b] have pointed out the very favorable effect on lichen urticatus secured by the use of parathyroid extract administered intramuscularly. They explain the good effect as one largely upon

calcium metabolism, but in view of this observation of Ferannini's, it is conceivable that the action of the parathyroid extract is by way of a reduction of blood sugar and a carbohydrate depletion of tissues rather than through the calcium metabolism. Cantarow, Brundage and Housel[6] have, moreover, shown that the intravenous injection of calcium gluconate and calcium levulinate, the former often used in urticarial and skin inflammatory conditions, likewise is followed by a decrease in blood sugar from 10 to 31 mg. per 100 cc. within 5 to 15 minutes. It would appear thus that a variety of agents, including parathormone and calcium salts (and perhaps even the act of intravenous injection itself?) may lead to changes in the blood sugar and consequently of its mobilization in tissue with influence on the water content, and behavior under inflammation-inducing circumstances.

That carbohydrate intake influences fat secretion by the skin and hence the seborrheic group of dermatoses is supported by the work of Rosenfeld, Kuznitsky and Birk. Rosenfeld,[58] by extracting the daily output of sebaceous secretion absorbed by clean woolen underwear, showed that a diet rich in carbohydrate produces more oily secretion than one rich in fat. This was confirmed by the work of Kuznitsky[37] and Birk.[3] It is interesting in this connection that Wile, Eckstein and Curtis[76] noted involution of xanthoma in a mild diabetic on a diet low in carbohydrate and relatively increased in fats, while the lipemia increased and the tumors became more numerous when sugar was increased in the diet.

The local excretion of carbohydrate in sweat has developed an as yet not completely evaluated significance for skin infections through the studies of Usher,[73] Usher and Rabinowitch[74] and of Cornbleet.[11a,c] Usher and Rabinowitch found that in patients with diminished sugar tolerance there was an increased excretion of dextrose in the sweat after intravenous injection of dextrose, but that it was due apparently simply to an increased volume of the sweat itself. Usher's work suggested that an increase in the sugar content of the sweat of diabetics led perhaps to more favorable conditions for the growth of bacteria and fungi. In studying the bactericidal properties of the skin, Cornbleet[11a] found that sugars produced a loss in the self-sterilizing powers of the skin because of fluctuations in the blood sugar level, and the retarded rate of return to the fasting level. This occurs in diabetics with a high blood sugar but may also occur in certain normal persons who thus become a prey to cutaneous infections. This loss in sterilizing power, according to Cornbleet, can be prevented by avoiding the ingestion of large quantities of carbohydrates at one time. In investigating reducing substances in the sweat in the yeast dermatoses, Cornbleet[11c] sweated patients in an electric light cabinet and found that the victims of yeast infections secreted smaller amounts of sweat than normal persons, thus producing an artefact of increased glucose concentration on their skins. While the occasion for the greater concentration of reducing substances in the sweat of persons with yeast infections is not known, Cornbleet regards the fact as undoubted, and attributes to this increased concentration of reducing substance at least a part of the increased susceptibility to fungus infection. Cornbleet found, moreover, a direct relation between the concentration of sugar in the sweat and that in the blood stream, and that administration of sugar by mouth had a definite effect on the content of reducing substances in

the sweat. The group with yeast infections showed a somewhat greater change in the content of sweat reducing substances after the ingestion of 50 gm. of dextrose than did the control group. He was not, however, successful in influencing materially the concentration of sweat reducing substances by attempts to reduce the blood sugar level.

The vitamin problem is also entangled with carbohydrate metabolism through several suggestive researches. Robertson[57] in 1934 reviewed the general question of vitamins and resistance to infection. Eddy and Dalldorf[16] point out that Funk[23] first called attention to the more rapid production of polyneuritis in animals deprived of vitamin B if the diets were rich in carbohydrate, and Peters, Kydd and Eisenman[51] feel that there is little doubt that recorded observations are indicative of a specific effect of vitamin B_1 upon carbohydrate metabolism. This influence is in their opinion not due merely to the general nutritional disturbance which accompanies the avitaminotic diet. But as in all speculation regarding vitamins, it sometimes seems as if a vitamin stick could always be found with which to beat the symptomatic dog. Carbohydrate tolerance and the bacterial flora of the gastro-intestinal tract are both quite markedly influenced by bowel motility (see Owles above) which in its turn is materially influenced by one of the known physiologic actions of vitamin B_1. It may accordingly be conceivable that the suggested action of vitamin B_1, as such, upon carbohydrate metabolism consists as much in hurrying the stuff through the intestinal tract in a stimulated peristalsis as in influencing the postabsorption carbohydrate metabolism as such. It is known, moreover, that vitamin B_1 in some way influences susceptibility to intestinal infections, and it may be that this effect on the bacterial content of the intestinal tract is the essential point of the application of the B_1 influence in carbohydrate metabolism. Be that as it may, there is reason to believe that vitamin B_1 materially influences some of the systemic effects of carbohydrate, and for that reason it may be a factor in behavior of the inflamed skin.

The Influence of Water Metabolism. Much that has been said in relation to carbohydrate metabolism has anticipated the following brief discussion of recent knowledge of the influence of water metabolism on skin inflammation. Following through the theoretical possibilities raised by Pillsbury and Kulchar's experimental work with glucose and sodium chloride administered parenterally in rabbits, Kulchar and Alderson[36] studied directly the effects of dehydration in rabbits on experimentally induced infections in their skins. They found that the dehydration not only did not unfavorably influence even to the point of lethal exit, the course of an artificially induced infection in the rabbit's skin, but that many animals apparently checked their infections, or at least the inflammatory manifestations disappeared, as they were deprived of water. In the reverse direction, when water was restored, the inflammation once more took up its full and even exaggerated activity. This series of observations confirms for the skin the now quite well established concept previously summarized that inflammatory reaction in the skin is profoundly influenced by water content.

This conception, not always with rational appreciation of its mechanism, has markedly influenced certain types of dermatologic treatment in the past few years. The most obvious method of reducing hydration of skin tissues is to reduce the intake of the salt primarily responsible for the retention of water in the skin; namely, sodium chloride. The

low salt diets, of which the Gerson-Hermannsdorfer-Sauerbruch diet is the most conspicuous example, probably have other modes of operation besides their dehydrating effect. Nonetheless, their inflammation-reducing properties are so striking and their applicability so definitely extending beyond the original field of tuberculosis treatment, that the common factor of their dehydrating effect seems the best all-around explanation of their usefulness. Gerson's[24] insistence on the predisposition to inflammation and particularly to infective inflammation, which he rates as characteristic of the allergically predisposed individual, may be related to the acid base equilibrium and thus to the water balance of the involved tissues. It is thus possible to explain the clinical usefulness of low salt diets and diets swinging sharply towards the acid-ash side, in the treatment of a variety of eczematous inflammatory processes (Zitzke and Peters[77]). Just as a sharp reduction in carbohydrate intake will dehydrate, so a marked increase of protein intake (essentially an acid-ash diet calculated to remove chlorine and potassium ions from tissue) will act as an effective dehydrator through the induced diuresis. The acid-ash and high protein as well as the low carbohydrate diets may then be regarded as effective instruments for skin dehydration and their reported favorable action on eczemas explained to some extent in this way.

It is further interesting that salt and water, as Johnston and Maroney[30] have pointed out, have an important relation to the carbohydrate metabolism previously discussed, in that they are important factors in the oxidation of dextrose. These investigators point out, for example, that blood sugar rises after the administration of acid, and remains normal or diminishes after the administration of alkali. Their probably most suggestive generalization is that optimal oxidation of dextrose may be thought of as taking place slightly on the acid side of neutrality, and slightly on the concentrated side of normal as far as hydration goes. Applying this conception to the previously cited observations of Menkin on the importance of local pH due to lactic acid in inflammatory manifestations, it is conceivable that when optimal pH and concentration is maintained in the blood stream or body tissues at large, the general bodily utilization of available dextrose will reach its highest point and its storage in tissue will perhaps be reduced to a minimum. Accordingly, in theory, "idle" glucose, so to speak, should not on an acid trend and moderate tissue dehydration be available in the skin for the lactic acid rôle in inflammatory manifestations described by Menkin.

An important group of acidosis or "acid trend" inducing agents (using acidosis in a therapeutic sense, so to speak) are such acids as hydrochloric acid and such readily dissociable salts as ammonium chloride. To the administration of dilute hydrochloric acid by mouth is quasi-empirically ascribed the correction of gastric secretory deficiency and intestinal pH abnormality which influences the allergic and the intestinal carbohydrate intolerance phenomena in cutaneous disease. On the other hand, there is every reason to suppose from the existing experimental background that liberal doses of hydrochloric acid perform an important part of their function by dehydrating the patient and thus reducing the inflammatory reactivity of his skin. It is rather interesting, therefore, that fruit taken in large quantities, though classed as alkaline-ash food, has likewise a dehydrating effect. This effect of fruit develops from the elimination of carbonates formed

in the breakdown of organic acids which combine with the alkaline constituents including metallic ions other than sodium which are present in the blood, tissues, and in the fruit juices themselves.

An interesting collateral of the water balance influence on cutaneous infections concerns cyclical menstrual exacerbations of such conditions as acne. The observation that immediately preceding menstruation women accumulate water in their tissues, is supported by numerous authors (Thomas,[70] Sweeney,[67] Molnar and Gruber,[46] Atkinson and Ivy,[2] Eufinger and Spiegler,[17] Okey and Stewart,[49] and Thorn, Nelson, and Thorn[71]). These authors have shown that a generalized edema regularly occurs in association with menstruation. In about one-third of the cases studied by some of these authors, there was an increase in weight and a swelling of the hands and feet at or about the time of menstruation. In most cases a rapid reduction occurred during menstruation. This corresponds to the time when the highest concentrations of estrogenic substance occur in the urine (Smith and Smith[61]) 12 days preceding menstruation (at or about the time of ovulation and the premenstrual period). Krohn and Zuckerman,[34] in studying water metabolism and the menstrual cycle in monkeys, found that the amount of water retained by the animal during the phase of swelling agreed closely with the observed increase in body weight. Heilig,[25] and Petersen and Milles[52] noted evidence of retention or delayed elimination of water and salts in the premenstrual period as compared with the intermenstrual period. Various explanations have been given for this delay in water excretion. Földes, recalling that Hasselbach and Bokelman and Rother noted an accumulation of acid substances in the body during pregnancy and the premenstrual period, believes that this accumulation may account for the water retention. In the latest work on this subject, Thorn, Nelson and Thorn (February, 1938) confirm this retention of water, sodium and chloride in human subjects during the intermenstrual as well as during the premenstrual period. They also were able to induce this retention in dogs by the injection of crystalline preparations of estrone, progesterone, pregnanediol and testosterone. In humans, the "onset of menstruation was associated with an increased renal excretion of sodium, chloride and water. Normal subjects, in whom no dietary restrictions were imposed, were observed to gain weight during the intermenstrual as well as during the premenstrual phase of the cycle. An increase in appetite and thirst was a striking symptom noted during the premenstrual period. The increase in the secretion of sex hormones and the increase in appetite and thirst appear," according to these authors, "to be contributing factors in body weight gain, which occurs during the menstrual cycle." It is quite possible that the effect of this retained water on inflammatory manifestations in the skin is the explanation of the monthly relapse annoyance in acne and acneiform eruptions.

The Influence of Vitamins. Whoever ventures to talk vitamin factors in cutaneous disease enters upon a territory in which confusion borderlines, cross effects and absence of adequate controls are as conspicuous as in the field of the clinical effects of endocrine preparations. The individual letter-denominated vitamins are in many cases complexes whose individual elements have more than one physiologic action. Until, therefore, the individual primitive extracted vitamin substances are replaced by synthetics which can be made the subject of adequate study in man as well as in the laboratory, confusion and uncertainty

of statement must be the rule. Distinction must, moreover, be drawn, in all discussion of vitamin therapy, between the effects of deficiency of so-called normal vitamin intake, whose definition appears to vary with each discussor, and often fails of definition entirely; and the effect of hypervitaminosis or the therapeutic administration of amounts far in excess of the ordinary dietary content.

When these considerations are kept in mind one is reduced to a discussion of vitamin A, vitamin C and certain components of the B complex insofar as effect on cutaneous inflammation and infection are concerned. No form of skin inflammation appears to be directly attributable to lack of vitamin A. Avitaminosis A in man, as studied by Frazier and Hu,[22] Loewenthal,[39] Pillat,[53] and Nichols,[48] is responsible however, for a follicular keratodermia or keratosis with dryness and scaling of the skin which apparently reduces its resistance to microorganisms present on the surface, and predisposes particularly to pyogenic infections.

Swift[68] maintains that vitamin A is essential to the normal keratization of the muco-cutaneous surfaces, and that deficiency leads to the development of kraurosis vulvæ and leukoplakia, and to the pruritus associated with them. He blames the hypochlorhydria of the elderly women in whom these conditions occur, for their failure to absorb vitamin A even from diets which are adequate in this respect. It is interesting to note here how many actions might be attributed to such a procedure as the administration of hydrochloric acid by mouth. It could influence the local infection situation with secondary pruritus through dehydration and through acidification of the urine with a change in pH of the involved mucous surfaces. Yet it is credited with its good effect through the absorption of vitamin A. Simpson and Mason,[60] in 30 cases of senile vaginitis, both in elderly and castrated women, found that the administration of vitamin A in the form of halibut liver oil and cod-liver oil resulted in restoration of the vaginal epithelium to normal. Kulchar,[35] who has recently reviewed the literature on vitamin A deficiency in relation to infection, cites Findlay's observation[19] that avitaminosis A leads to a reduction in lysozyme in the tear secretion of rats sufficient to permit the growth of staphylococci and the establishment of infections about the eyes. Hill and White,[27] and Fleming[20] have demonstrated similar ferment-like substances in the skin, whose dependence on vitamin A deficiency has not, however, been studied. From this angle one finds another conceivable explanation of the apparent increase in pyogenic infections in individuals suffering from vitamin A deficiency. Additional suggestive evidence on the definite increase in resistance of the skin of infants receiving adequate amounts of vitamin A has been accumulated by MacKay[40] and by Clausen.[9a,b] That avitaminosis A, as such, is responsible for increased susceptibility to pyogenic infection in rats, was negated by the work of Sternberg and Pillsbury,[62] who found that this particular avitaminosis had no influence upon the course of a standardized experimental pyogenic infection in these animals.

The possible influence of vitamin C on inflammations and infections has been anticipated from its known importance to capillary physiology; from certain observations such as those of Höjer[29] on the effect of scurvy on the course of tuberculosis in guinea pigs, particularly in the matter of scar formation; and from a number of observations, beginning with

those of Heise and Martin[26] that there is a markedly reduced excretion of vitamin C in the urine of tuberculous individuals, from which it is inferred that a larger amount of it is fixed or utilized in the defense against the tuberculous process. Important influences on the course of diphtheria have also been observed. This general information on the subject is not paralleled by anything in the way of an adequate study of the influence of vitamin C on cutaneous infection. The one present striking example of the importance of vitamin C in skin inflammation is that of arsphenamine dermatitis, in which Sulzberger and Oser[66] and Mayer and Sulzberger[41] who preceded them, claim credit for the observation that large doses of vitamin C inhibit arsphenamine sensitization in guinea pigs. Chapman and Morrell[8] reported that guinea pigs on a diet high in vitamin C developed marked sensitization reactions to neoarsphenamine, while pigs on a low vitamin C diet developed a less marked sensitivity. Cormia[10] found that variations in the vitamin C content of the diet of guinea pigs ranging from 0.025 to 0.2 mg. cevitamic acid had little influence on the development of cutaneous arsphenamine hypersensitiveness, but that a low vitamin C diet increased the intensity of reactions to the initial dose of neoarsphenamine, and retarded their involution. Large doses of vitamin C given for one week before a second test injection had little sensitivity-inhibiting effect. Further experimental work by this author indicated that guinea pigs which were unsensitizable during a summer period, sustained in a considerable proportion later flare reactions to intracutaneously injected neoarsphenamine as evidence of sensitization produced by a low vitamin C diet. Cormia's series apparently showed that the vitamin C content of the summer diet is what provides protection against neoarsphenamine sensitization, and that it can be artificially produced by 2 weeks of vitamin C deficiency. Huge doses of cevitamic acid entirely prevented the sensitization of 22 guinea pigs to neoarsphenamine. Previous and subsequent observations by Dainow,[15] Vanthey,[75] and Landfisch[38] indicated that cevitamic acid is an effective desensitizer in a variety of allergic conditions and that it is particularly influential in preventing arsphenamine dermatitis. Landfisch, for example, treated 25 patients, to whom an arsphenamine preparation could not be given safely, with synthetic cevitamic acid in ampules in doses of 0.05 gm. dissolved in 10 cc. of water and in tablet form for oral administration. Of the 25 patients, 12 male and 13 female, the evidence of intolerance disappeared in 11 male and 9 female patients (80%). In 4 female patients (16%), slight symptoms of intolerance were observed, and 1 male patient (4%) remained intolerant.

Cornbleet[11b] has also shown as likewise in the case of vitamin A that vitamin C has a pigment reducing effect on the skin which was first manifest in patients with Addison's disease, and is probably related to the presumed deficiency of vitamin C in the adrenal cortex of such patients. Cornbleet states that pigment and vitamin C occur together in the skin, and that the pigment is apparently the anchor that holds the vitamin C. If pigment is not present, vitamin C is not stored in the skin in demonstrable amounts. In this particular, the action of vitamin C is antagonistic to that of copper, which hastens the darkening and precipitation of di-oxy-phenyl-allanin by ultra-violet light.

The influence of vitamin D on cutaneous inflammation is as yet virtually unknown territory. Through its influence on the absorption

of calcium from the intestinal tract, viosterol may conceivably influence the course of cutaneous inflammation and affect skin irritability. The only direct therapeutic effect which is sufficiently clear-cut to suggest a sound causal background is the reported action of very large doses of vitamin D on psoriasis. The favorable influence of sunlight on psoriasis has long been empirically known. Ceder and Zon,[7] recognizing a possible rational explanation in the formation of vitamin D in the skin by sunlight, proceeded to use the vitamin in treatment in place of the sunlight. While the results as yet lack confirmation, they are very suggestive. These investigators treated 15 cases of chronic widespread psoriasis by 300,000 to 400,000 units of vitamin D from irradiated ergosterol daily. Eleven of the 15 cases obtained complete involution in a maximum of 12 weeks; 2 obtained a partial benefit and 2 showed no benefit. Apparently in the hands of these authors massive doses of the preparations used appeared to be relatively safe when administered to adults.

There remain to be considered as vitamin factors in skin inflammations, the various components of the B complex. Vitamin B_1, through its action on intestinal motility and carbohydrate metabolism may, as previously discussed, conceivably influence cutaneous inflammation. The recently recognized presence in the B complex of an achlorhydria-inhibiting factor is of some importance to those who ascribe to hypo- and achlorhydria important relations to the intestinal carbohydrate tolerance syndrome and its cutaneous vascular expressions, including rosacea. Since the influence of the "P-P" fraction of vitamin B is no longer under dispute, it is not discussed here. A supposedly specific anti-dermatitic factor in the B complex has been variously designated as "B_6," "Factor Y" and "vitamin H." It appears to be an element separate from the "P-P" antipellagra fraction, and its deficiency is responsible for the appearance of dermatitis in rats, affecting first the paws and the tips of the ears and nose. Milbradt,[45] of Leipzig, describes three types of widely differing rat dermatosis produced by lack of this vitamin "H," the third type resembling seborrheic dermatitis. He considers that there are essential differences between the avitaminotic dermatitis of rats and seborrheic eczema in man. Thus far the therapeutic application of vitamin H to the treatment of human seborrheic dermatitis has proved disappointing.

Thus far it appears, then, that high vitamin therapy, insofar as it concerns cutaneous inflammatory disease, has a not too highly specific and in fact rather shotgun quality concerned mainly (and especially in the case of the B complex) with the effect of the vitamins on the general constitution and nutrition of patients. The two nearest approaches to a specific use are found for vitamin A in keratodermic disturbances and their associated pyogenic infections, and in senile vaginitis and pruritus vulvæ; and for vitamin C in allergic dermatitic disturbances of the skin, particularly the prevention of arsphenamine cutaneous sensitization.

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PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF FEBRUARY 21, 1938

The Effect of Dead Optic Vesicle on Explanted Gastrular Ectoderm. C. D. Van Cleave (Laboratory of Anatomy, University of Pennsylvania). The influence of dead optic vesicle upon explants of prospective ectoderm of early gastrulæ and of body ectoderm from late neurulæ of *Amblystoma punctatum* was studied in these experiments exclusively by the explantation method. An ether extract of dead optic vesicles induced neither lens nor other structures in explanted body ectoderm of neurulæ. No inductions were obtained in explants of body ectoderm of neurulæ containing one dead optic vesicle. Explanted fragments of prospective ectoderm differentiated as epidermis. Explants of prospective ectoderm containing 2 to 6 dead optic vesicles were killed by this amount of dead material. Of 41 explants of prospective ectoderm containing one dead optic vesicle 17 showed inductions of definite neural character after 7 days' cultivation. Pattern and organization were lacking in the induced masses; entodermal and mesodermal rudiments were not observed. In 3 such explants the induced structures resembled optic rudiments and lentoids connected with a brain mass. The tentative conclusion is drawn that the influence of the dead optic vesicle may be imposed on the indifferent ectoderm. The results of similar experiments of Lopashov and of Holtfreter are discussed.

The Effect of Prontosil and Related Compounds Upon the Chemotropism of Leukocytes. Dale Rex Coman (Laboratory of Pathology, University of Pennsylvania). The purpose of these experiments was to determine whether or not substances of the sulphanilamide group increase chemotropism of leukocytes and in this way exert their therapeutic action.

The chemotropic effects of prontosil, sulphanilamide and setazine were studied by noting the response *in vitro* to these substances by rabbit neutrophils. Prontosil-soluble was adsorbed on kaolin, carbon, and hemolytic streptococci respectively. Control preparations of kaolin, carbon and streptococci were also studied. Sulphanilamide and setazine were used in crystalline form. The paths of leukocytes were followed under the microscope, as they moved in relation to these substances. The measure of chemotropism adopted was the number of micra per minute the cells moved toward the test substance. Prontosil did not significantly alter the chemotropic response of the leukocytes. Sulphanilamide, in the concentration employed, resulted in a cessation of cell movement. Setazine caused only slight positive chemotropism.

From these experiments it is considered unlikely that the therapeutic effect of these compounds is due to increased chemotropism of leukocytes.

Sulphanilamide in Experimental Streptococcic Meningitis. PAUL E. ADOLPH and JOHN S. LOCKWOOD (Laboratory of Surgical Research, University of Pennsylvania). Streptococcic encephalo-meningitis was produced in white rats by introducing the organisms into a traumatized subarachnoid space through a trephine opening in the skull. A fragment of agar was left in contact with the meninges to serve as a propagating nidus. The disease in controls was characterized by rapid onset of signs of meningeal irritation, death invariably ensuing within about 48 hours. Animals given 150 mg. of sulphanilamide once daily for 5 days did not survive much longer than controls. Those given 75 mg. twice daily for 5 days showed marked increase in survival rate (57%), and at the same time failed to display characteristic clinical signs of meningitis. In this group, the average length of life of those dying was about 7 days. Eighty per cent of the controls had hemolytic streptococci in the heart blood postmortem, whereas only 11% of the treated group showed this evidence of invasive infection. Examination of histological material revealed that the outstanding difference between control and treated animals (either those dying or those sacrificed) was the absence of evidence of tissue invasion in the latter group. Seventy-four per cent of control rats showed large numbers of free cocci in meningeal exudates, whereas only 36% of treated animals showed many free cocci, and in half of these the organisms were confined to a localized abscess. Control animals did not live long enough to develop abscesses. Sixty-three per cent of control animals showed cocci invading the cortex and meninges in advance of cellular exudate, while none of treated animals evidenced such invasion. From these experiments one might conclude that the principal effect of sulphanilamide is prevention of invasion.

Conclusions. Sulphanilamide given by mouth is capable of inducing marked alteration in the clinical and pathological course of experimental streptococcic meningitis. The effect of the drug seems to be to minimize invasion of blood stream and tissues.

The Cardiac Arrhythmia, Characteristic Effect of Thiobarbiturates, as Influenced by Changes in Arterial Blood Pressure. CHARLES M. GRUBER, VICTOR G. HAURY and CHARLES M. GRUBER, JR. (Laboratory of Pharmacology, Jefferson Medical College). The effects of intravenous injections in anesthetic doses of pentothal sodium, sodium thiopentobarbital and thio-ethamyl were studied in 68 dogs. In these, cardiac arrythmia was produced in every animal, after either the first or the second injection. If, after the injection of the thio-barbiturates in anesthetic doses, the rhythm of the heart remained normal, or had returned to normal, the increased blood pressure due to inactivation of one carotid sinus (by occlusion of the common carotid) initiated the cardiac arrhythmia in 70% of the experiments. Cutting both vagi had no influence on the effect of carotid occlusion in producing this cardiac arrhythmia in animals under thio-barbiturate anesthesia.

Atropine sulphate, picrotoxin and metrazol injected intravenously did not affect the arrhythmia. Ouabain, tyramine and ephedrine, on the other hand, when injected into dogs under thio-barbiturate anesthesia, initiated cardiac arrhythmia in every instance. Intravenous

epinephrine caused the arrhythmia to disappear. Acetylcholine when given intravenously caused the dipsapearance of the arrhythmia in all animals in which atropine sulphate was not previously injected. In those experiments in which atropine was injected, acetylcholine was ineffective.

Histamine acid phosphate, quinidine sulphate, amyl nitrite, and glyceryl trinitrate restored the regular rhythm to the heart. This we believe to be due to the decrease in blood pressure. Hemorrhage likewise will convert cardiac arrhythmias due to thio-barbiturates to a normal rhythm.

The Rôle of the Cervical Nerves in Facial Sensations. F. H. LEWY (Departments of Physiology and Surgery, University of Pennsylvania). The normal sensibility of the face was tested in normal persons and in patients with unilateral trigeminal neuralgia. In the latter, tests were also made on the pathological side both before and after subtotal section of the fifth nerve root. Frequency curves in which the threshold values of the touch points are plotted against the number of incidences of responses, show two maxima, the one at 15 volts, the other at 40 volts. After section of the fifth nerve root, the maximum at 15 volts disappears while the maximum at 40 volts remains unchanged. Frequency curves of the time factor of touch sensations show a similar two-peaked curve. The first of these two peaks disappears after section of the fifth nerve root. It is inferred from these observations that the touch points having a low mechanical and electrical threshold and a low time factor are innervated by the fifth nerve, those having high values are supplied by the cervical segments. The frequency curve of the time factor to painful stimuli has only one maximum. The majority if not all pain points within the area of the fifth nerve seem to be supplied by the fifth nerve only. The disturbance of pain sensibility after subtotal section of the fifth nerve is characterized by complete disappearance of some pain points—penalgesia. Those points that remain show a high threshold—hypalgesia.

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